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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 3	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 4	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 5	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 6	JAN 22	CA/CAplus updated with revised CAS roles
NEWS 7	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS 8	JAN 29	PHAR reloaded with new search and display fields
NEWS 9	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 10	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS 11	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS 12	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS 13	FEB 26	MEDLINE reloaded with enhancements
NEWS 14	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS 15	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS 16	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 17	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS 18	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS 19	MAR 16	CASREACT coverage extended
NEWS 20	MAR 20	MARPAT now updated daily
NEWS 21	MAR 22	LWPI reloaded
NEWS 22	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS 23	APR 02	JICST-EPLUS removed from database clusters and STN
NEWS 24	APR 30	GENBANK reloaded and enhanced with Genome Project ID field
NEWS 25	APR 30	CHEMCATS enhanced with 1.2 million new records
NEWS 26	APR 30	CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS 27	APR 30	INPADOC replaced by INPADOCDB on STN
NEWS 28	MAY 01	New CAS web site launched

NEWS EXPRESS	NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:47:03 ON 02 MAY 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:47:13 ON 02 MAY 2007
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 1 MAY 2007 HIGHEST RN 934050-43-8
DICTIONARY FILE UPDATES: 1 MAY 2007 HIGHEST RN 934050-43-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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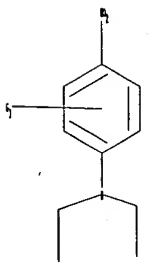
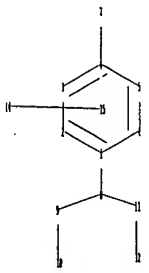
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10529772\Struc 1.str





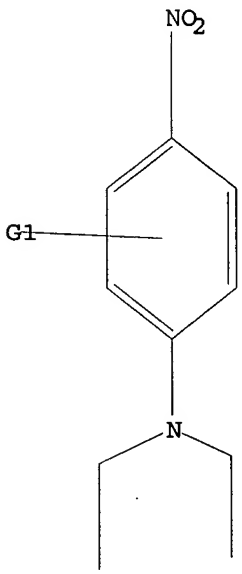
chain nodes :
7 8 9 10 11 12 14
ring nodes :
1 2 3 4 5 6
chain bonds :
1-8 4-7 8-9 8-11 9-10 11-12
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6
exact/norm bonds :
1-8 8-9 8-11
exact bonds :
4-7 9-10 11-12
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

G1:CN,SO2,NO2

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:CLASS 14:CLASS 15:Atom

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 CN,SO2,NO2

Structure attributes must be viewed using STN Express query preparation.

=> l1
SAMPLE SEARCH INITIATED 09:47:28 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 521 TO ITERATE

100.0% PROCESSED 521 ITERATIONS 32 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9051 TO 11789
PROJECTED ANSWERS: 301 TO 979

L2 32 SEA SSS SAM L1

=> l1 full
FULL SEARCH INITIATED 09:47:31 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 9870 TO ITERATE

100.0% PROCESSED 9870 ITERATIONS 604 ANSWERS
SEARCH TIME: 00.00.01

L3 604 SEA SSS FUL L1

=> file medline caplus
COST IN U.S. DOLLARS SINCE FILE TOTAL

	ENTRY	SESSION
FULL ESTIMATED COST	172.10	172.31

FILE 'MEDLINE' ENTERED AT 09:47:42 ON 02 MAY 2007

FILE 'CAPLUS' ENTERED AT 09:47:42 ON 02 MAY 2007

=> l3
L4 320 L3

=> d scan

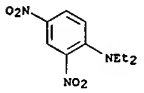
L4 320 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN
CC 25-6 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
TI Dinitroanilines as antiparasitic compounds, their preparation, pharmaceutical compositions, and use to treat parasite infections
ST nitroaniline prepn antiparasitic
IT Caenorhabditis
(CB5161; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(Chagas' disease; preparation of dinitroanilines as antiparasitic compds.)
IT Caenorhabditis
(DF5070; preparation of dinitroanilines as antiparasitic compds.)
IT Caenorhabditis
(PS1010; preparation of dinitroanilines as antiparasitic compds.)
IT Caenorhabditis
(SB341; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(aerosols; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(ascariasis; preparation of dinitroanilines as antiparasitic compds.)
IT Medical goods
(biodegradable; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(blastocystosis; preparation of dinitroanilines as antiparasitic compds.)
IT Protozoa
(blood; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(carriers; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(cryptosporidiosis; preparation of dinitroanilines as antiparasitic compds.)
IT Parasite
(ecto-; preparation of dinitroanilines as antiparasitic compds.)
IT Parasite
(endo-; preparation of dinitroanilines as antiparasitic compds.)
IT Cestoda
Coccidia
(enteric; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(filariasis; preparation of dinitroanilines as antiparasitic compds.)
IT Protozoa
(flagellates, enteric; preparation of dinitroanilines as antiparasitic compds.)
IT Nematoda
(gastrointestinal; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
Intestine, disease
(giardiasis; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(hookworm; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(implants, controlled-release; preparation of dinitroanilines as antiparasitic compds.)
IT Toxocara
(infection from, toxocariasis; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(inhalants; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(injections, i.m.; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(injections, i.v.; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(leishmaniasis; preparation of dinitroanilines as antiparasitic compds.)
IT Biodegradable materials
(medical; preparation of dinitroanilines as antiparasitic compds.)
IT Eye, disease
(ocular onchocerciasis; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(oral; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(parasitic; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(parenterals; preparation of dinitroanilines as antiparasitic compds.)
IT Acrosternum acutum
Amidostomum
Amidostomum fulicae
Ancylostoma
Antimalarials
Blastocystis hominis
Boreostrongylus
Boreostrongylus minutes
Boreostrongylus seurati
Caenorhabditis briggsae
Caenorhabditis drosophilae
Caenorhabditis elegans
Caenorhabditis japonica
Caenorhabditis maupasi
Caenorhabditis plicata
Caenorhabditis remanei
Caenorhabditis sonorae
Caenorhabditis vulgarensis
Coccidiosis
Coccidiostats
Cryptosporidium
Cryptosporidium andersoni
Cryptosporidium baileyi
Cryptosporidium canis
Cryptosporidium felis
Cryptosporidium galli
Cryptosporidium hominis
Cryptosporidium meleagridis
Cryptosporidium molnari
Cryptosporidium muris
Cryptosporidium parvum
Cryptosporidium saurophilum
Cryptosporidium serpentis
Cryptosporidium wrairi
Dirofilaria
Dirofilaria immitis
Echinococcus
Echinococcus granulosus
Echinococcus multilocularis
Echinococcus oligarthrus
Echinococcus vogeli
Eimeria
Filaria
Filarinema
Giardia
Giardia lamblia
Heligmonina
Heligmonina nevoi
Hookworm
Leishmania
Leishmania aethiopica
Leishmania braziliensis
Leishmania donovani
Leishmania donovani infantum
Leishmania major
Leishmania mexicana
Leishmania peruviana
Leishmania tropica
Malaria
Nematospiroides dubius
Nippostrongylus
Nippostrongylus brasiliensis
Nippostrongylus witenbergi
Onchocerca
Onchocerca volvulus
Parasiticides
Pediculus humanus capitis
Pediculus humanus corporis
Plasmodium (malarial genus)
Plasmodium falciparum
Prophylaxis
Pthirus pubis
Sarcoptes scabiei
Schistosoma haematobium
Schistosoma japonicum
Schistosoma mansoni
Taeniidae
Tenorastrongylus
Tenorastrongylus josephi
Toxocara canis
Toxocara cati
Toxoplasma gondii
Trichomonas vaginalis
Trichostrongylus
Trichostrongylus colubriformis
Trypanosoma
Trypanosoma brucei
Trypanosoma cruzi
Trypanosoma rhodesiense
Wuchereria
Wuchereria bancrofti
(prepn. of dinitroanilines as antiparasitic compds.)
IT Infection
(river blindness; preparation of dinitroanilines as antiparasitic compds.)
IT Skin, disease
(scabies; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(schistosomiasis; preparation of dinitroanilines as antiparasitic compds.)
IT Cestoda
Nematoda
(systemic; preparation of dinitroanilines as antiparasitic compds.)
IT Drug delivery systems
(topical; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(toxoplasmosis; preparation of dinitroanilines as antiparasitic compds.)
IT Infection
(trypanosomiasis; preparation of dinitroanilines as antiparasitic compds.)
IT 912587-97-4P, 1-Morpholino-2,4-dinitro-6-(trifluoromethyl)benzene 912587-98-5P, 1-Thiomorpholino-2,4-dinitro-6-(trifluoromethyl)benzene 912587-99-6P, 1-(4-Acetyl-1-piperazinyl)-2,4-dinitro-6-(trifluoromethyl)benzene 912588-00-2P, 1-(4-Ethyl-1-piperazinyl)-2,4-dinitro-6-(trifluoromethyl)benzene 912588-01-3P, 1-[4-(2-Pyrimidyl)-1-piperazinyl]-2,4-dinitro-6-(trifluoromethyl)benzene 912588-02-4P, N-(2-Morpholinoethyl)-2,4-dinitro-6-(trifluoromethyl)aniline 912588-03-5P, 1-[4-(1-Pyrrolidinyl)-1-piperidinyl]-2,4-dinitro-6-(trifluoromethyl)benzene 912588-04-6P, 1-(4-Methyl-1-piperazinyl)-2,4-dinitro-6-(trifluoromethyl)benzene 912588-05-7P, N-Cyclopentyl-2,4-dinitro-6-(trifluoromethyl)aniline 912588-06-8P, N-Cyclopentyl-N-methyl-2,4-dinitro-6-(trifluoromethyl)aniline 912588-07-9P 912588-08-0P 912588-09-1P 912588-10-4P 912588-11-5P 912588-12-6P 912588-13-7P 912588-14-8P 912588-15-9P 912588-16-0P 912588-17-1P 912588-18-2P 912588-19-3P 912588-20-6P 912588-21-7P 912588-22-8P 912588-23-9P 912588-24-0P 912588-25-1P 912588-26-2P 912588-27-3P 912588-28-4P 912588-29-5P 912588-30-8P 912588-31-9P 912588-32-0P 912588-33-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of dinitroanilines as antiparasitic compds.)
IT 110-91-8, Morpholine, reactions 123-90-0, Thiomorpholine 392-95-0, 2-Chloro-3,5-dinitrobenzotrifluoride 2038-03-1, 4-(2-Aminoethyl)morpholine 5004-07-9, 4-(1-Pyrrolidinyl)piperidine 5308-25-8, 1-Ethylpiperazine 13889-98-0, 1-Acetylpiperazine 20980-22-7, 1-(2-Pyrimidyl)piperazine
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of dinitroanilines as antiparasitic compds.)
IT 912865-98-6 912865-99-7 912866-00-3
RL: PRP (Properties)
(unclaimed nucleotide sequence; dinitroanilines as antiparasitic

L4 320 ANSWERS CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
compds., their prepn., pharmaceutical compns., and use to treat parasite infections)

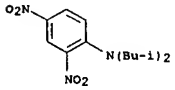
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d ibib abs hitstr 301-320

L4 ANSWER 301 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1946:15147 CAPLUS
DOCUMENT NUMBER: 40:15147
ORIGINAL REFERENCE NO.: 40:2921g-h
TITLE: Toxicity tests of certain N-substituted 2,4-dinitroanilines on codling moth larvae
AUTHOR(S): Siegler, E. H.; Gertler, S. I.
CORPORATE SOURCE: Natl. Research Center, Beltsville, MD
SOURCE: Journal of Economic Entomology (1945), 38, 708-9
CODEN: JEENAI; ISSN: 0022-0493
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB In laboratory tests with newly hatched Carpocapsa pomonella larvae, the following compds. in this series gave 89% or less of wormy apples: 2,4,4'-trinitrodiphenylamine 54; N,N-diethyl-2,4-dinitroaniline 75; N,N-diisobutyl-2,4-dinitroaniline 83; N-isobutyl-2,4-dinitroaniline 84; N-ethyl-2,4-dinitroaniline 87; N-isopropyl-2,4-dinitroaniline 89. The lead arsenate control gave 63.
IT 837-64-9, Aniline, N,N-diethyl-2,4-dinitro- (in cod ling-moth control)
RN 837-64-9 CAPLUS
CN Benzenamine, N,N-diethyl-2,4-dinitro- (9CI) (CA INDEX NAME)

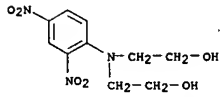


IT 100879-48-9, Diisobutylamine, N-(2,4-dinitrophenyl)- (in codling-moth control)
RN 100879-48-9 CAPLUS
CN Aniline, N,N-diisobutyl-2,4-dinitro- (6CI) (CA INDEX NAME)

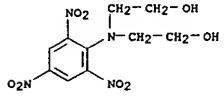


L4 ANSWER 302 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1939:23428 CAPLUS
DOCUMENT NUMBER: 33:23428
ORIGINAL REFERENCE NO.: 33:3341d-i
TITLE: Interaction of di(β-hydroxyethyl)amine, methylamine and ethylamine on halonitrobenzenes
AUTHOR(S): Waldkotter, K. F.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1939), 58, 132-8
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 33, 1286.9. 2,4-(O2N)2C6H3Cl and (HOCH2CH2)2NH (I) in EtOH, refluxed 5 hrs., give 2,4-dinitro-1-(di-β-hydroxyethylamino)benzene, yellow, m. 99°; it has a bitter taste; di-Ac derivative, golden yellow, m. 77°; HNO3 yields a di-nitrate ester, 2,4-(O2N)2C6H3N(CH2CH2ONO2)2, m. 103°. I and picryl chloride give a mixture of 2,4,6-trinitro-1-(di-β-hydroxyethylamino)benzene (II), 2,4,6-(O2N)3C6H2N(CH2CH2OH)2, yellow, m. 245° (decomposition), and the picryl ester (III) of I, 2,4,6-(O2N)3C6H2OCH2CH2NHCH2CH2OH, yellow, m. 154°, separated by recrystn. from H2O, II being the less soluble III with HNO3 gives picric acid; II gives the mono-nitrate ester, 2,4,6-(O2N)3C6H2N(CH2CH2OH)CH2CH2ONO2, m. 198°. 1,3,4,6-Cl2C6H2(NO2)2 and I, refluxed in EtOH for 3 hrs., give 4,6-dinitro-1,3-bis(di-β-hydroxyethylamino)benzene, orange, m. 126°; it has a bitter taste. The following compds. were obtained by reacting NO2 compds, with MeNH2 or EtNH2 and acetylating and nitrating the resulting products. 4,2-Cl(O2N)C6H3 NH2: 1-acetylmethyl derivative, m. 92°; 1-acetylethyl derivative, m. 47°. 4,2,6-Cl(O2N)2C6H2NH2: 1-acetylmethyl derivative, m. 134°; 1-Et derivative, orange, m. 101°; 1-acetylethyl derivative, pale yellow, m. 73°. 4,2-Br(O2N)C6H3NH2: 1-acetylmethyl derivative, m. 116°; 1-acetylethyl derivative, yellow, m. 57°. 4,2,6-Br(O2N)2C6H2NH2: 1-acetylmethyl derivative, pale yellow-green, m. 103°; 1-Et derivative, orange, m. 90°; 1-acetylethyl derivative, pale yellow-green, m. 91°. 5,2-Cl(O2N)C6H3NH2: 1-acetylmethyl derivative, pale yellow, m. 87°; 1-acetylethyl derivative, pale green, m. 108°. 5,2-Br(O2N)C6H3NH2: 1-acetylmethyl derivative, colorless m. 112°; 1-acetylethyl derivative, pale yellow-green, m. 129°. 4,6,1,3-(O2N)2C6H2(NH2)2: di-Me derivative, with 1 mole EtOH, yellow, m. 160-70°; di(acetylmethyl) derivative, pale yellow, m. 173°; di-Et derivative, with 1 mole EtOH, yellow, m. 90-110°; di(acetylethyl) derivative, deep yellow, m. 108°. 4,6,2-Cl2(O2N)C6H2NH2: 1-acetylmethyl derivative, colorless, m. 60°; 1-methylnitro derivative, colorless, m. 72°; 1-Et derivative, orange, m. 61°; 1-ethylnitro derivative, pale yellow, m. 96°. 4,6,2-Br2(O2N)C6H2NH2: 1-acetylmethyl derivative, colorless, m. 89°; 1-Et derivative, orange, m. 74°; 1-ethylnitro derivative, an oil. The effect of various groups on color is discussed. The taste of most of the NH2 compds. becomes bitter on introduction of 1 or more NO2 groups. The bitter taste is somewhat suppressed to faintly bitter or tasteless by the presence of 1 or more CH2CH2OH groups.
IT 5246-88-8, Ethanol, 2,2'-(2,4-dinitrophenylimino)di- (and derivs.)
RN 5246-88-8 CAPLUS

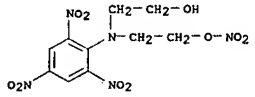
L4 ANSWER 302 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Ethanol, 2,2'-[(2,4-dinitrophenyl)imino]bis- (9CI) (CA INDEX NAME)



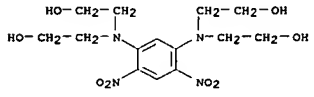
IT 114303-58-1P, Ethanol, 2,2'-(picrylimino)di- 854224-96-7P , Ethanol, 2,2'-(picrylimino)di-, mononitrate (ester) 854225-59-5P , m-Phenylenediamine, N,N,N',N'-tetrakis(2-hydroxyethyl)-4,6-dinitro- RL: PREP (Preparation) (preparation of)
RN 114303-58-1 CAPLUS
CN Ethanol, 2,2'-(picrylimino)di- (6CI) (CA INDEX NAME)



RN 854224-96-7 CAPLUS
CN Ethanol, 2,2'-(picrylimino)di-, mononitrate (ester) (4CI) (CA INDEX NAME)



RN 854225-59-5 CAPLUS
CN Ethanol, 2,2',2'',2'''-(4,6-dinitro-m-phenylenedinitrilo)tetra- (4CI) (CA INDEX NAME)



L4 ANSWER 302 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L4 ANSWER 303 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1939:8651 CAPLUS
DOCUMENT NUMBER: 33:8651
ORIGINAL REFERENCE NO.: 33:1287g-i,1288a-i,1289a
TITLE: Derivatives of 1,3-bis(phenylamino)propane
AUTHOR(S): Veer, W. L. C.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1938), 57, 989-1015
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: English

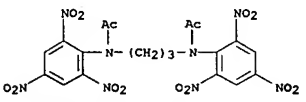
AB CH2(CH2Br)2 and PhNH2 give CH2(CHNHPh)2 (I), bll 244-5°, m. 40-1°, nD20 1.6144; it quickly becomes yellow in the light and finally turns brown; it has antioxidant properties for rubber but does not protect it against aging under atmospheric conditions or against the action of O3 when under tension. The residue from I, the structure of which is unknown, gives I on distillation at 200-40° in an absolute vacuum. I yields the following derivs.: HCl salt, m. 144°; sulfate, m. 157°; nitrate, m. 155-6° (decomposition) or 123° (block); N-NO derivative, yellowish brown, m. 86°; N-di-Ac derivative (II), m. 119°; N-di-Bz derivative, m. 135°; N-di-carbomethoxy derivative, m. 69°; N-di-carbethoxy derivative, m. 56°. I does not react with CS2 to give a thiocarbamate or thiourea derivative I and MeNCO in C6H6 at room temperature give 1,3-bis(1'-phenyl-3'-methylureido)propane, m. 153-5°, with a bitter taste; PhNCO gives the 1'-phenyl-3'-phenylureido derivative, m. 154-7°; MeCNS gives the 1'-phenyl-3'-methylthioureido derivative, m. 151°; ketene gives II. C3O2 and I in Et2O give 1,5-diphenyl-6,8-diketo-1,5-diazacyclooctane, m. indefinitely at 117°. I gives no definite product with 2,4-(O2N)2C6H3Cl or with 2,4,6-(O2N)3C6H2Cl in MeOH or EtOH, with or without AcONa. I and 33% HCHO at 40-50° give 1,3-diphenylhexahydropyrimidine, m. 87°; 1,2,3-tri-Ph derivative, m. 120°; 1,3-diphenyl-2-(4'-chlorophenyl) derivative, m. 89°; 1,3-diphenyl-2-(4'-nitrophenyl) derivative, m. 130°; 1,3-diphenyl-2-α-furyl derivative, m. 138.5°. These are decomposed by acids into the 2 components. I does not react with AcH, EtCHO, 2-HOC6H4CHO, 4-MeOC6H4CHO, 4-HOC6H4CHO or 5-methylfurfuraldehyde. I and HNO3 at 0° give 1,3-bis [(2',4',6'-trinitrophenyl)-nitramino] propane (III), pale yellow, m. 189°. The preparation of CH2(CH2NH2)2 (IV) is discussed. It results in 41% yield from CH2(CH2Br)2 and liquid NH3 (ratio 1:3) in an autoclave for 24 h. IV and o-ClC6H4NO2 in EtOH, heated 8 h. at 140°, give 33.6% of the 2'-nitrophenyl derivative, orange; it could not be prepared from CH2(CH2Br)2 and o-O2NC6H4NH2, either on heating at 150-60°, in EtOH at 140-50° or in a sealed tube with C5H5N at 120-30°; the Ac derivative is a sticky mass; nitration gives III. The 4'-nitrophenyl derivative of IV, yellow, m. 196°; di-Ac derivative (V), pale yellow, m. 170°; nitration gives III. 2',4'-Dinitrophenyl derivative of IV, yellow, m. 233°, bitter taste; di-Ac derivative, m. 121°; nitration gives III. 2',4',6'-Trinitrophenyl derivative of IV, yellow, m. 199°, bitter taste; di-Ac derivative, with 0.5 mol dioxane, m. 151°; nitration gives III.

L4 ANSWER 303 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Hydrolysis of III gives picric acid. Nitration of II gives V. (p-MeC6H4NHCH2)2CH2 (VI), m. 69-70°, yields a di-Ac deriv., m. 120°; the 3'-phenylthioureido analog, with 1 mol EtOH, m. 152-4°. VI and 33% HCHO at 80-90° for 1 h. give 1,3-di(4'-methylphenyl)hexahydropyrimidine, cream, m. 60-3°; 1,3-di(4'-methylphenyl)-2-(4'-nitrophenyl)hexahydropyrimidine, orange (from EtOH) or red (from light petroleum), m. 155°; VI does not react with BzH. Nitration of VI gives 1,3-bis[N-(4'-methyl-2',6'-dinitrophenyl)nitramino]propane (VII), pale yellow, m. 173°, decomps. 174-5°. 4,2,6-Me(O2N)2C6H2OMe and CH2(CH2NH2)2 in EtOH give 1,3-bis(4'-methyl-2',6'-dinitrophenylamino)propane, golden yellow, m. 206°; di-Ac deriv., yellowish green, m. 184°; nitration gives VII, m. 181°. 1,2-Bis(4'-methyl-2',6'-dinitrophenylamino)ethane, orange, m. 233°; nitration gives the nitramino deriv., m. 230°. CH2(CH2Br)2 and p-ClC6H4NH2 with AcONa, heated at 100-10°, give 1,3-bis (4'-chlorophenylamino)propane, m. 75°; di-Ac deriv., m. 128°; nitration gives 1,3-bis[(N-4'-chloro-2',6'-dinitrophenyl)-nitramino]propane (VIII), m. 159°, highly explosive. 4,2,6-Cl(O2N)2C6H2OMe and IV in EtOH give 1,3-bis(4'-chloro-2',6'-dinitrophenylamino)propane, orange-red or pale yellow, m. 217°; di-Ac deriv., pale yellow, m. 204°; nitration gives VIII. 1,3-Bis(4'-bromophenylamino)propane, from CH2(CH2Br)2 and p-BrC6H4NH2 in EtOH on refluxing 7 h., m. 96°; di-Ac deriv., m. 134°; HNO3 gives 1,3-bis[N-(4'-bromo-2',6'-dinitrophenyl)nitramino]propane (IX), cream, m. 167°; 1,3-bis(4'-bromo-2',6'-dinitrophenylamino)propane, yellow, m. 194°; di-Ac deriv., pale yellow, m. 190°; nitration gives IX. 3,4-(O2N)2C6H3Cl and IV, refluxed in EtOH for 1 h., give 1,3-bis (5'-chloro-2'-nitrophenylamino)propane (X), orange, m. 205°; the Ac deriv. did not crystallize; nitration gives 1,3-bis[N-(5'-chloro-2',4',6'-trinitrophenyl)nitramino]propane (XI), m. 100°, highly explosive. The 5'-Br analog of X, orange, m. 226°; di-Ac deriv., m. 137°; 5'-Br analog of XI, m. 117°, highly explosive. 1,3,4,5-Cl2C6H2(NO2)2 and C2H4(NH2)2 in EtOH give 1,2-bis(4',6'-dichloro-2'-nitrophenylamino)ethane (XII), orange-red, m. 135°; di-Ac deriv., pale yellow-green, m. 242°; HNO3 gives the nitramino deriv., pale yellow, m. 196°. 4',6'-Di-Br analog of XII, orange, m. 134°; di-Ac deriv., m. 251°; nitramino deriv., pale yellow, m. 207°. 1,3-Bis (4',6'-dichloro-2'-nitrophenylamino)propane, orange, m. 124°; di-Ac deriv., pale yellow-green, with 1 mol MeOH, m. 163°; nitramino deriv., pale yellow, with 0.5 mol EtOH, m. 149°, slightly explosive. 4',6'-Di-Br analog, orange, m. 138°; di-Ac deriv., with 1 mol MeOH, m. 155°; nitramino deriv., m. 199°. Qual. data for the soly. of many of these compds. are given for H2O, EtOH, Me2CO, Et2O, petr. ether, C6H6, PhMe, CHCl3, CCl4, AcOH, AcOEt, PhNO2 and dioxane.

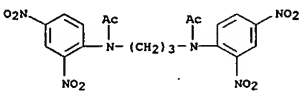
IT 857620-82-7P, Acetanilide, N,N'-trimethylenebis[2,4,6-trinitro-
857620-85-0P, Acetanilide, N,N'-trimethylenebis[2,4-dinitro-
RL: PREP (Preparation)
(preparation of)

RN 857620-82-7 CAPLUS
CN Acetanilide, N,N'-trimethylenebis[2,4,6-trinitro- (4CI) (CA INDEX NAME)

L4 ANSWER 303 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 857620-85-0 CAPLUS
CN Acetanilide, N,N'-trimethylenebis[2,4-dinitro- (4CI) (CA INDEX NAME)



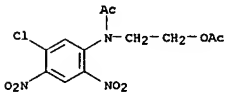
L4 ANSWER 304 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1939:8650 CAPLUS
DOCUMENT NUMBER: 33:8650
ORIGINAL REFERENCE NO.: 33:1286i,1287a-g
TITLE: Interaction of β-hydroxyethylamine and halonitrobenzenes
AUTHOR(S): Waldkotter, K. F.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1938), 57, 1294-1310
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HOCH2CH2NH2 (I) and 2,4-(O2N)2C6H3Cl give 2,4-(O2N)2C6H3NHCH2CH2OH (IA), yellow-orange, m. 90° (C. A. 32, 5798.8 gave 175-6°, which is the m. p. of 2,4-(O2N)2C6H3NH2); Ac2O and H2SO4 give the N-Ac derivative, deep yellow, m. 130°. Nitration of IA gives 2,4,6-(O2N)3C6H2N(NO2)CH2CH2ONO2 (II), m. 129° (this is also termed pentryl). Picryl chloride and 2 equivs. of I in EtOH or 1 equivalent of I and AcONa in EtOH give 2,4,6-(O2N)3C6H2NHCH2CH2OH (III), yellow, m. 110°, bitter taste; the di-Ac derivative, pale yellow, m. 117°. Nitration of III gives II. I and 2,1,4-O2NC6H3Cl2 in EtOH, heated 5 h. at 140-5°, give 4-chloro-2-nitro-1-(β-hydroxyethylamino)benzene, orange, m. 107°; di-Ac derivative, pale yellow, m. 48°; absolute HNO3 at -15° gives N-(4-chloro-2,6-dinitrophenyl)-N-nitro-β-aminoethyl nitrate (IV) m. 90°; it is explosive, decomps. at 105° and ignites at 296°; on the Maquenne block it m. 81° and then at 92°. 4-Chloro-2,6-dinitroanisole and I in EtOH, heated 2 h., give 4-chloro-2,6-dinitro-1-(β-hydroxyethylamino)benzene, orange, m. 102°; nitration yields IV. 2,1,4-O2NC6H3Br2 and I give 4-bromo-2-nitro-1-(β-hydroxyethylamino)benzene, deep orange, m. 106°, faintly bitter taste; di-Ac derivative, yellow, m. 53°; nitration gives N-(4-bromo-2,6-dinitrophenyl)-N-nitro-β-aminoethyl nitrate (V), m. 95°, decomps. 180°, ignites 256°. 4-Bromo-2,6-dinitroanisole and I give 4-bromo-2,6-dinitro-1-(β-hydroxyethylamino)benzene, orange, m. 114°, with a bitter taste; nitration yields V; V does not react in the expected manner with EtOH-NH4OH or with EtOH-KOH. 3,4-(O2N)2C6H3Cl and I in EtOH, boiled 2 h., give 5-chloro-2-nitro-1-(β-hydroxyethylamino)benzene, orange-red, m. 116°, with a faintly bitter taste; di-Ac derivative, pale yellowish green, m. 94°; absolute HNO3 at -10° gives N-(5-chloro-2,4-dinitrophenyl)-N-nitro-β-aminoethyl nitrate (VI), yellow, decomps. 180°, ignites 253°. 4,6,1,3-(O2N)2C6H2Cl2 and I in EtOH, refluxed 1.5 h., giving 5-chloro-2,4-dinitro-1-(β-hydroxyethylamino)benzene, golden yellow, m. 132°; a 2nd modification (?) m. 116°; di-Ac derivative, m. 96°; nitration gives VI. 3,4-(O2N)2C6H3Br and I gives 5-bromo-2-nitro-1-(β-hydroxyethylamino)benzene (VII), yellow, m. 126°, faintly bitter taste; di-Ac derivative, pale yellow-green, m. 75°; hydrolysis by boiling with H2O for 0.5 h. gives the N-Ac derivative, golden yellow, m. 109°. Absolute NHO3 and VII at -10° give N-(5-bromo-2,4-dinitrophenyl)-N-nitro-β-aminoethyl nitrate, m. 114°, decomps. 173°, ignites 262°. 4,6,1,3-(O2N)2C6H2Cl2 and 4 equivs. of I in EtOH give 4,6-dinitro-1,3-bis(β-hydroxyethylamino)benzene (VIII), orange-yellow, m. 211°, with a bitter taste; 2 equivs. of I and AcONa gave unsatisfactory results; di-N-Ac derivative, pale yellow, m.

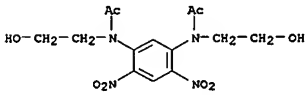
L4 ANSWER 304 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
149°. VIII does not yield a cryst. NO2 deriv. 4,5,1,3-(O2N)2C6H2Cl2 and I in EtOH, heated 3 h., give 4,6-dichloro-2-nitro-1-(β-hydroxyethylamino)benzene, reddish orange, m. 51°, tasteless; di-Ac deriv., pale yellow, m. 82°; abs. HNO3 gives N-(4,6-dichloro-2-nitrophenyl)-N-nitro-β-aminoethyl nitrate, m. 88°, decomps. 187°, ignites 305°.
4,6-Dibromo-2-nitro-1-(β-hydroxyethylamino)benzene, orange-red, m. 71°, tasteless; di-Ac deriv., pale yellow, m. 86°; nitration yields N-(4,6-dibromo-2-nitrophenyl)-N-nitro-β-aminoethyl nitrate, pale yellow, m. 69°, decomps. 178°, ignites 305°.

IT 855876-46-9P, Acetanilide, 5-chloro-N-2-hydroxyethyl-2,4-dinitro-, acetate 855881-64-0P, Acetamide, N,N'-(4,6-dinitro-m-phenylene)bis[N-2-hydroxyethyl- 857622-21-0P, Acetanilide, N-2-hydroxyethyl-2,4,6-trinitro-, acetate 857622-24-3P, Acetanilide, N-2-hydroxyethyl-2,4-dinitro-
RL: PREP (Preparation)
(preparation of)

RN 855876-46-9 CAPLUS
CN Acetanilide, 5-chloro-N-2-hydroxyethyl-2,4-dinitro-, acetate (4CI) (CA INDEX NAME)

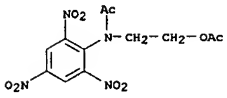


RN 855881-64-0 CAPLUS
CN Acetamide, N,N'-(4,6-dinitro-m-phenylene)bis[N-2-hydroxyethyl- (4CI) (CA INDEX NAME)

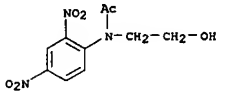


RN 857622-21-0 CAPLUS
CN Acetanilide, N-2-hydroxyethyl-2,4,6-trinitro-, acetate (4CI) (CA INDEX NAME)

L4 ANSWER 304 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 857622-24-3 CAPLUS
CN Acetanilide, N-2-hydroxyethyl-2,4-dinitro- (4CI) (CA INDEX NAME)



L4 ANSWER 305 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1938:24315 CAPLUS
DOCUMENT NUMBER: 32:24315
ORIGINAL REFERENCE NO.: 32:3395a-i,3396a-d
TITLE: Symmetrical secondary diamines derived from 1,2-diaminoethane
AUTHOR(S): Rameau, J. Th. L. B.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1938), 57, 192-214
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: English

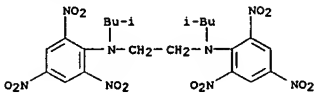
AB (CH2NH2)2 and p-MeOC6H4CHO give (CH2N:CHPh)2 which is reduced by Na and EtOH to 1,2-bis(p-methoxybenzylamino)ethane (I), b21 275°, m. 30-2°, nD15 1.5680; HCl salt, decomps. about 150°; alkaline KMnO4 gives p-MeOC6H4CHO. I reacts with aldehydes with the formation of tetrahydroimidazole derivs. 1,3 - Bis(p-methoxybenzyl)tetrahydroimidazole, m. 30°; 2-Me derivative, m. 76-7°; 2-Ph derivative, m. 93-4°; 2-p-methoxyphenyl derivative, m. 73°; 2-(3',4'-methylenedioxyphenyl) derivative, m. 120°; 2-benzyl derivative, m. 68-9°; 2-(2'-furfuryl) derivative, m. 76°; 2-(5'-methyl-2'-furfuryl) derivative, m. 84°; 2-(5'-hydroxymethyl-2'-furfuryl) derivative, m. 108°; all the compds. are decomposed by dilute HCl into I-HCl and the corresponding aldehyde.
I yields a di-Ac derivative, m. 151-2°; di-Bz derivative, m. 182°; this is suitable for identifying I; NO derivative, m. 105°; I and MeNCO give 1,2-bis(1'-p-methoxybenzyl-3'-methylureido)ethane, m. 153-4°; Ph analog, m. 187°. Boiling I and 2,4-(O2N)2C6H3Cl in EtOH for 1 h. gives the 2',4'-dinitrophenyl derivative of I, orange, m. 184°; in boiling AcOH the p-MeOC6H4CH2 groups are split off, giving [(O2N)2C6H3NHCH2]2; 2',4',6'-trinitrophenyl derivative, orange, m. 205°. I and C3O2 in Et2O at 0° give 1,4-bis(p-methoxybenzyl)-5,7-dioxo-1,4-diazacycloheptane, liquefies at 90° and decomps. at higher temps. I in 60% HNO3 gives the nitrate, I.2HNO3, decomps. about 100°; in absolute HNO3 at -10° there results the dinitrate, pale yellow, decomps. about 150°, of 1,2-bis(4'-methoxy-3',5'-dinitrobenzylamino)ethane, orange, m. 91-2°; under certain conditions there results a di-NO2 derivative On reduction of the condensation product of (CH2NH2)2 and PhCH2CHO (2 mols.) with Na and EtOH there results about 5% of 1-(2'-phenylethylamino)-2-aminoethane (II), b12 120-5°, and 1,2-bis(2'-phenylethylamino)ethane (III), b12 195-200°; 10% yields may be obtained from (CH2NH2)2 and PhCH2CHO in Et2O; reaction of (CH2Br)2 and PhCH2CH2NH2 (boiling 1 h., adding KOH and boiling a further 10 min.) gives 70% of III, b28 255-60°, nD11.5 1.5600; HCl salt, decomps. about 50°. II yields a di-Bz derivative, m. 124°; PhNCO gives the bis(3'-phenylureido) derivative, m. 169-70°; the bis-[3'-(1''-naphthyl)ureido] derivative, amorphous, becomes viscous at 90°. Aldehydes and III give the following: 1,3-bis(2'-phenylethyl)tetrahydroimidazole, b12 160-80°, nD20 1.5560; 2-Me derivative, pale yellow, b21 230-60°, nD24.5 1.5790; 2-(p-methoxyphenyl) derivative, b15 210-30°, nD21 1.5774; 2-(2'-furfuryl) derivative, pale yellow, b15 240-55°, nD17 1.5644; 2-(5'-methyl-2'-furfuryl) derivative, pale yellow, b15 250-65°, nD12 1.5680. The b. ps. were not accurately determined because of the small amount available. III gives a di-Ac derivative, b12 285-95°, nD22 1.5580;

L4 ANSWER 305 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
di-Bz deriv., m. 194°; di-NO deriv., m. 82-3°; 3'-phenylureido deriv., m. 111°; 3'-(1''-naphthylureido) deriv., m. 152-3°; 2',4'-dinitrophenylamino deriv., yellow, m. 187°; 2',4',6'-trinitrophenylamino deriv., brownish red, decomps. 235°.
1,2-Bis(2'-methylpropylamino)ethane (IV), b. 212°, nD19 1.4375; di-HCl salt, decomps. 130°; aldehydes give the following: 1,3-bis(2'-methylpropyl)tetrahydroimidazole, b28 70-80°, nD24 1.4430; 2-Me deriv., b28 65-85°, nD22.5 1.4470; 2-iso-Pr deriv., b22 90-100°, nD24 1.4470; 2-Ph deriv., pale yellow, b20 180°, m. 45-6°; 2-(p-methoxyphenyl) deriv., pale yellow, b25 130-60°, nD23.5 1.5094; 2-(3',4'-methylenedioxyphenyl) deriv., m. 61°; 2-(2'-furfuryl) deriv., b22 100-20°, nD24.5 1.4750; 2-(5'-methyl-2'-furfuryl) deriv., b22 130-55°, nD24 1.4744; 2-(5'-hydroxymethyl-2'-furfuryl) deriv., m. 56-7°. IV forms a di-Ac deriv., pale yellow, b20 170-80°, nD25 1.4720; di-Bz deriv., m. 127°; di-NO deriv., m. 87°; bis(3'-phenylureido) deriv., m. 173-4°; bis[3'-(1''-naphthyl)ureido] deriv., m. 235°; bis(2',4'-dinitrophenylamino) deriv., yellow, m. 157°; bis(2',4',6'-trinitrophenylamino) deriv., orange, m. 196-7°.
(CH2NH2)2 and 2 mols. furfuraldehyde give 1,2 - bis(2' - furfurylmethyleneamino)ethane (V), b30 205°, m. 53-4°; redn. gives 1,2-bis(2'-furfurylmethylamino)ethane (VI), b20 190°, nD18 1.5200; HCl salt, decomps. about 100°; if the V is not purified there also results 1-(2'-furfurylmethylamino)-2-aminoethane (VII), b17 140-4°; di-Bz deriv. of VII, m. 148°; bis(3'-phenylureido) deriv., m. 162-3°; bis[3'-(1'-naphthylureido) deriv., m. 183°. VI and aldehyde give the following: 1,3-bis(2'-furfurylmethyl)tetrahydroimidazole, pale brown, b24 100-20°, nD18 1.5265; 2-Me deriv., pale yellow, b18 75-95°, nD12.5 1.5280; 2-Ph deriv., b24 190-5°, nD19 1.5630; 2-(p-methoxyphenyl) deriv., pale yellow, b18 220-40°, nD12.5 1.5650; 2-(2''-furfuryl) deriv., pale yellow, b20 180-95°, nD12 1.5460; 2-(5''-methyl-2''-furfuryl) deriv., pale yellow, b20 190-210°, nD12.5 1.5440. VI yields a di-Ac deriv., pale yellow, b18 225-35°, m. 88°; di-Bz deriv., m. 142°; di-NO deriv., m. 79°; bis(3'-phenylureido) deriv., m. 174°; bis[3'-(1''-naphthyl)ureido] deriv., m. 178°; bis(2',4'-dinitrophenylamino) deriv., yellow, m. 155°; bis(2',4',6'-trinitrophenylamino) deriv., brownish red, m. 150°.
The method of prepg. di-sec-diamines from (CH2NH2)2, by condensing the latter with aldehydes and reducing the reaction product, only gives good results when the intermediate condensation product can be isolated and purified.

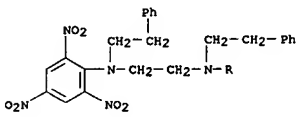
IT 854245-49-1P, Ethylenediamine, N,N'-diisobutyl-N,N'-dipicryl- 854246-23-4P, Ethylenediamine, N,N'-diphenethyl-N,N'-dipicryl- 854246-46-1P, Ethylenediamine, N,N'-bis(2,4-dinitrophenyl)-N,N'-diphenethyl- 854246-49-4P, Ethylenediamine, N,N'-bis(2,4-dinitrophenyl)-N,N'-diisobutyl-
RL: PREP (Preparation)
(preparation of)

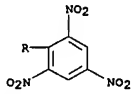
RN 854245-49-1 CAPLUS
CN Ethylenediamine, N,N'-diisobutyl-N,N'-dipicryl- (4CI) (CA INDEX NAME)

L4 ANSWER 305 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

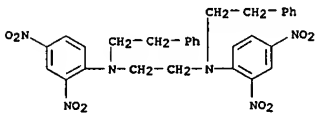


RN 854246-23-4 CAPLUS
CN Ethylenediamine, N,N'-diphenethyl-N,N'-dipicryl- (4CI) (CA INDEX NAME)



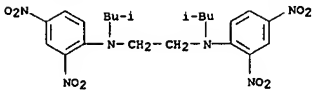


RN 854246-46-1 CAPLUS
CN Ethylenediamine, N,N'-bis(2,4-dinitrophenyl)-N,N'-diphenethyl- (4CI) (CA INDEX NAME)



RN 854246-49-4 CAPLUS
CN Ethylenediamine, N,N'-bis(2,4-dinitrophenyl)-N,N'-diisobutyl- (4CI) (CA INDEX NAME)

L4 ANSWER 305 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L4 ANSWER 306 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN

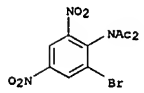
ACCESSION NUMBER: 1937:38059 CAPLUS
DOCUMENT NUMBER: 31:38059
ORIGINAL REFERENCE NO.: 31:5335h-i,5336a-d
TITLE: Nitration and halogenation of 1,2-bis(phenylamino)ethane and its derivatives. I
AUTHOR(S): Schouten, A. E.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1937), 56, 541-61
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Details are given for the preparation of (CH2NHPh)2 and its acetylation and nitration, of (CH2NHC6H4NO2-2)2 and its acetylation and nitration, of (CH2NHC6H4NO2-4)2 (N-Ac derivative, pale yellow, m. 217°) and its nitration, of (CH2NHC6H3(NO2)-2,4)2 (N-Ac derivative, golden-yellow, m. 234°) and its nitration, and of (CH2NHC6H2(NO2)3-2,4,6)2 (Ac derivative, pale yellow, m. 242°) and its nitration. Heating o-ClC6H4NH2 and C2H4Br2(2:1) with AcONa for 6 h. at 150° gives 1,2-bis-(2-chlorophenylamine)ethane, m. 69°; N-Ac derivative, m. 188°; nitration gives the N-(2-chloro-4,6-dinitrophenyl)-nitramino derivative (I), m. 238°; the structure follows from the following synthesis: 1,2,4-Cl2C6H3NO2 and C2H4Br2 give 1,2-bis(2-chloro-4-nitrophenylamino)ethane, yellow, m. 308° (N-Ac derivative, m. 232°); nitration gives I. 1,2-Bis(2-chloro-4,6-dinitrophenylamino)ethane, yellow-brown, m. 172° (N-Ac derivative, m. 293°); nitration gives I. 1,2-Bis(2-bromophenylamino)ethane, m. 76°; N-Ac derivative, m. 192°; N-(2-bromo-4,6-dinitrophenyl)nitramino derivative (II), m. 240°. 1,2-Bis(2-bromo-4-nitrophenylamino)ethane, yellow, m. 319°; N-Ac derivative, m. 264°; nitration gives II. 1,2-Bis-(2-bromo-4,6-dinitrophenylamino)ethane, golden-yellow, m. 156°; N-Ac derivative, m. 308°; nitration gives II. 2-Bromo-4,6-dinitrodiacetanilide, m. 110°; 2-bromo-4,6-dinitroacetanilide, m. 235°. 1,2-Bis(4-chlorophenylamino)ethane, m. 99°; N-Ac derivative, m. 138°; N-(4-chloro-2,6-dinitrophenyl)nitramino derivative (III), m, 201°. 1,2-Bis(4-chloro-2-nitrophenylamino)ethane, orange-red, m. 253°; N-Ac derivative, m. 265°; nitration gives III. 1,2-Bis(4-chloro-2,6-dinitrophenylamino)ethane, orange-red, m. 222°; N-Ac derivative, pale yellow, m. 248°; nitration gives III. 1,2-Bis(4-bromophenylamino)ethane, m. 108°; N-Ac derivative, m. 158°; N-(4-bromo-2,6-dinitrophenyl)nitramino derivative (IV), m. 205°. 1,2-Bis-(4-bromo-2-nitrophenylamino)ethane, reddish brown, m. 247°; N-Ac derivative, m. 281°; nitration gives IV. 1,2-Bis-(4-bromo-2,6-dinitrophenylamino)ethane, m. 199°; N-Ac derivative, m. 225°; nitration gives IV. (CH2NHC6H4Me-4) on nitration gives the N-(4-methyl-2,6-dinitrophenyl)-nitramino derivative, m. 229°.

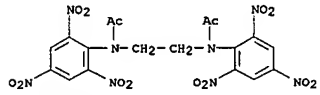
IT 854400-73-0P, Diacetanilide, 2-bromo-4,6-dinitro-
857622-58-3P, Acetanilide, N,N'-ethylenebis[2,4,6-trinitro-
857622-63-0P, Acetanilide, N,N'-ethylenebis[2,4-dinitro-
873411-05-3P, Acetanilide, N,N'-ethylenebis[2-bromo-4,6-dinitro-
873411-29-1P, Acetanilide, N,N'-ethylenebis[2-chloro-4,6-dinitro-
RL: PREP (Preparation)
(preparation of)

RN 854400-73-0 CAPLUS
CN Diacetanilide, 2-bromo-4,6-dinitro- (4CI) (CA INDEX NAME)

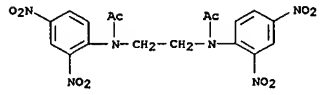
L4 ANSWER 306 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



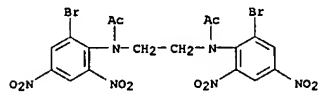
RN 857622-58-3 CAPLUS
CN Acetanilide, N,N'-ethylenebis[2,4,6-trinitro- (4CI) (CA INDEX NAME)



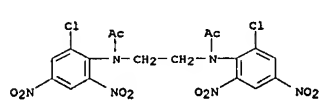
RN 857622-63-0 CAPLUS
CN Acetanilide, N,N'-ethylenebis[2,4-dinitro- (4CI) (CA INDEX NAME)



RN 873411-05-3 CAPLUS
CN Acetanilide, N,N'-ethylenebis[2-bromo-4,6-dinitro- (4CI) (CA INDEX NAME)



RN 873411-29-1 CAPLUS
CN Acetanilide, N,N'-ethylenebis[2-chloro-4,6-dinitro- (4CI) (CA INDEX NAME)



L4 ANSWER 306 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L4 ANSWER 307 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1936:45195 CAPLUS
DOCUMENT NUMBER: 30:45195
ORIGINAL REFERENCE NO.: 30:5992h-i,5993a-e
TITLE: Aliphatic polyamines. I
AUTHOR(S): van Alphen, J.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1936), 55, 412-18
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: English

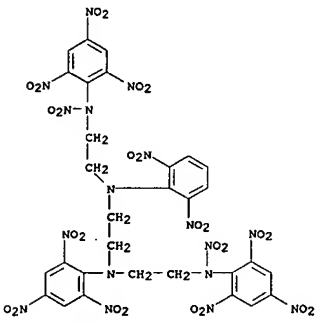
AB 1,2-Bis(aminoethylamino)ethane (I), the triethylenetetramine of Hofmann (Ber. 3, 762(1870); 4, 666(1871); 23, 3297, 3711(1890)) is prepared in good yield as follows: pour 150 g. (CH2Br)2 in 125 cc. absolute EtOH slowly into 250 g. of 1,2-diaminoethane hydrate in 125 cc. absolute alc., reflux 1 hr., add 250 g. solid KOH and continue heating 10 min., stand overnight, filter, distil at atmospheric pressure to 130°, cool. Distil the upper layer in vacuo. Two fractions are obtained: I, b31 174°, and 1-(aminoethylaminoethyl)-piperazine or tetraethylenetetramine (II), b31 266-70°. I loses its 0.5 mol. H2O when distilled at ordinary pressure and b. 272°. It is characterized by its tetra-Bz derivative m. 236° (from alc.). I yields the following derivs.: 1,2 - bis[3' - phenyl - 1' - [2'' - (3''' - phenylureido)-ethyl]ureido]ethane, m. 237°, by adding PhNCO in ether and recrystg. the precipitate from EtOH; 1,2-bis-(3'-phenyl-1'-[2''-(3'''-phenylthioureido) ethyl]thioureido]ethane, m. 206°, by mixing with PhNCS in absolute alc. and purifying the insol. precipitate by extracting with boiling alc.; 1,3-bis(2''-benzylidene-aminoethyl)-2-phenyltetrahydroimidazole, m. 86° (immediately decomposed by dilute HCl), from 14.6 g. I and 31.8 g. BzH; 1,2-bis-{[(2''',4'''-dinitrophenyl) [(2'',4''-dinitrophenylamino) ethyl]] amino} -ethane (III), m. 285°, by boiling 6.7 g. I, 5 g. 1-bromo-2,5-dinitrobenzene, 5 g. NaOAc and 20 cc. EtOH for 1 hr., extracting the amorphous precipitate with H2O and boiling alc., dissolving in hot Me2CO (from which it suddenly ppts. as crystals and is then insol.), and recrystg. from boiling PhNO2; 1,2-bis(3'-thiotetrahydroimidazole-1')-ethane, m. 265° (recrystd. from H2O), by mixing alc. I with alc. CS2 and heating the precipitate of yellow thiocarbamate which loses H2S at 120-40°; 1,2 - bis[[(2''',4''',6''' - trinitrophenyl) [(2'',4''6''-trinitrophenylnitramino)ethyl]]amino]-ethane, which decomposes at 165° and explodes when heated suddenly, was prepared from 0.5 g. III and 5 cc. HNO3 cooled to - 15°, and precipitated by adding ice water slowly. II, a strong base, is a pale yellow viscous liquid with tobacco-like smell, miscible with H2O and EtOH but not with Et2O. Its formula is proved by the formation of the following compds.: tetra-picrate, m. 212°, tetra-oxalate, m. 289°, tri-Bz derivative: 4-benzoyl-1-[2'-[(benzoyl) (2''-benzoylaminoethyl)-amino]ethyl]- piperazine, prepared by the Schotten-Baumann method but could not be

L4 ANSWER 307 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

crystd.; its di-picrate, m. 221°; 4 - phenylthiocarbamido - 1 - [2' - [(phenylthiocarbamido-[2'' - (3''' - phenylthioureido) ethyl]amino]ethyl) piperazine, m. 132-40° (decompn.) from the reaction of alc. II with alc. PhNCS and repeatedly extd. with boiling alc.; and the mono-Bz deriv., 1-(benzylaminoethylaminoethyl)-piperazine-H2O, m. 50° (recrystd. from H2O), prepd. by mixing 1 mol. of II with 2 mols. BzH, dissolving in abs. EtOH, adding 4 atoms Na, pptg. with strong HCl and treating with H2O and NaOH; its tetra picrate, m. 212° (decompn.).

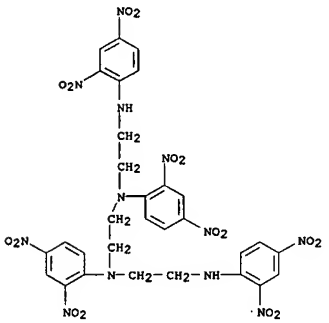
IT 858000-60-9P, Triethylenetetramine, N,N'-dinitro-N,N',N'',N'''-tetrapicryl- 858845-75-7P, Triethylenetetramine, N,N',N'',N'''-tetrakis(2,4-dinitrophenyl)-
RL: PREP (Preparation)
(preparation of)

RN 858000-60-9 CAPLUS
CN Triethylenetetramine, N,N'-dinitro-N,N',N'',N'''-tetrapicryl- (3CI) (CA INDEX NAME)



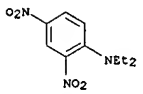
RN 858845-75-7 CAPLUS
CN Triethylenetetramine, N,N',N'',N'''-tetrakis(2,4-dinitrophenyl)- (3CI) (CA INDEX NAME)

L4 ANSWER 307 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

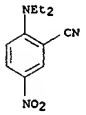


L4 ANSWER 308 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1934:945 CAPLUS
DOCUMENT NUMBER: 28:945
ORIGINAL REFERENCE NO.: 28:119a-i
TITLE: Reactivity of the chlorine atom in the benzene nucleus
AUTHOR(S): Dey, Biman Bihari; Doraiswami, Yetchan Gunja
SOURCE: J. Indian Chem. Soc. (1933), 10, 309-20
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The relative influences of the NO2, CN and CO2H groups on the reactivity of a Cl atom adjacent to each of these groups in an aromatic nucleus containing a NO2 group in addition to the halogen atom and an activating group have been investigated by a study of the condensations of 2,4-(O2N)2C6H3Cl (I), 2,4-NC(O2N)C6H3Cl (II) and 2,5-Cl(O2N)C6H3CO2H (III) with divers compds. The activating influence of the groups on the replacement of halogen by means of the aromatic amines decreases in the order NO2 > CO2H > CN. With NaOMe and NaOEt as well as with NHEt2 and urea the order becomes NO2 > CN > CO2H. It seems that, just as the order in which the different halogens are replaced depends upon the reagent used (C. A. 18, 674), so is the relative activating influence of the various neg. groups dependent largely on the nature of the reagents employed for substitution. Attempts to condense I, II and III with the Na derivs. of CH2(CO2Et)2 (IV), AcCH2CO2Et (V), NCCH2CO2Et, MeNO2 and NCCH2CONH2 (VI) were only successful in the cases of I with IV and V, and I and II with VI. The difference in behavior of halo-2-nitro-4-cyanobenzene and of halo-2-cyano-4-nitrobenzene toward these reagents (C. A. 11, 959) as well as toward the aromatic amines is another example of the superior influence of the NO2 when adjacent to the halogen atom. The reduction of II (3 g.) with Sn and HCl gave 2 g. 4-chloro-3-cyanoaniline, m. 133° (stable to concentrated H2SO4, concentrated HCl and to boiling aqueous and alc. KOH); Ac derivative m. 190°. Nitration of crude o-ClC6H4CO2H (20 g.) yielded 10-12 g. of III, m. 164°; Me ester (VII), m. 72°. By heating the components on the H2O bath quant. yields of the condensation products of I with PhNH2 and o-, m- and p-MeC6H4NH2, m. 158°, 118°, 160° and 135°, resp., were obtained. The condensation between II and PhNH2, m- and p-MeC6H4NH2 by heating the substances together at 180° for 45-60 min. gave compds. m. 171°, 140° and 217°. II and p-ClC6H4NH2, similarly treated, gave 2-cyano-4-nitro-4'-chlorodiphenylamine, m. 282°, but no condensation was effected with o-MeC6H4NH2 even when the components were heated at 200° for 2 h. When heated with PhNH2, III yielded 2-anilino-5-nitrobenzoic acid, m. 250°, converted by heating with PhNH2 at 160° for 30 min. into 2-anilino-5-nitrobenzamide, m. 190°. The condensation of VII with PhNH2 gave Me 2-anilino-5-nitrobenzoate, m. 100°. With o-, m- and p-MeC6H4NH2, III formed the corresponding 5-nitro-2-toluinobenzoic acids, m. 254°, 256° and 262°, resp. By boiling alc.

L4 ANSWER 308 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
NHEt2 with I and II were formed 2,4-dinitrodiethylaniline, m. 81°, and 2-cyano-4-nitrodiethylaniline, m. 88°, then condensed with I to produce 2,4-dinitroaniline, m. 176°, and with II to give 2-uramido-5-nitrobenzamide, m. 198°, hydrolyzed by 15% KOH heated to boiling for 30 min. to 5-nitroanthranilic acid (VIII), m. 264°, and to 5-nitrosalicylic acid when boiled vigorously with 20% KOH. VIII was prepd. by nitrating acetylanthranilic acid and deacetylating the 5-nitroacetylanthranilic acid, m. 214°, by boiling with concd. HCl for 30 min. o-, m- and p-ClC6H4NO2 did not react with urea. By refluxing I with NaOEt and NaOMe for 20-30 min. were formed 1-ethoxy- and 1-methoxy-2,4-dinitrobenzene, m. 86° and 89°. II similarly yielded 1-ethoxy- and 1-methoxy-2-cyano-4-nitrobenzene, m. 101° and 128° NaOEt and p-ClC6H4NO2 gave p-O2NC6H4OEt, m. 57°, and a byproduct, p,p'-dichloroazoxybenzene, m. 154°. No definite product could be isolated from attempts to condense NaOEt with o-ClC6H4NO2. By adding I to solns. of IV and V in alc. NaOEt and refluxing for 2-3 h., di-Et 2,4-dinitrophenylmalonate, m. 52°, and Et 2,4-dinitrophenylacetoacetate, m. 83°, were obtained.
IT 837-64-9P, Aniline, N,N-diethyl-2,4-dinitro- 81676-69-9P , Anthranilonitrile, N,N-diethyl-5-nitro-
RL: PREP (Preparation)
(preparation of)
RN 837-64-9 CAPLUS
CN Benzenamine, N,N-diethyl-2,4-dinitro- (9CI) (CA INDEX NAME)

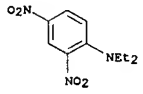


RN 81676-69-9 CAPLUS
CN Benzonitrile, 2-(diethylamino)-5-nitro- (9CI) (CA INDEX NAME)



L4 ANSWER 309 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1933:56542 CAPLUS
DOCUMENT NUMBER: 27:56542
ORIGINAL REFERENCE NO.: 27:5065a-e
TITLE: Reaction velocities of 1-chloro(bromo)-2,4-dinitrobenzene with aliphatic amines
AUTHOR(S): Blanksma, J. J.; Schreinemachers, H. H.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1933), 52, 428-36
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Previously van Romburgh has shown that the formation of alkylamino-2,4-dinitrobenzenes from 2,4-(O2N)2C6H3Br and aliphatic amines gives a good method for identifying amines (cf. Rec. trav. chim. 2, 31, 103(1883); 4, 189(1885)); the present paper deals with the reaction velocity of this reaction. The reaction was measured in absolute EtOH at 25°, the concentration of the amine being twice as great as that of the Cl(Br) compound; the reaction constant was calculated according to the equation: K = x/t(A - x)A, which follows from: dx/dt = k(A - x)(2A - 2x). The following reaction consts. were determined for 1-chloro- and 1-bromo-2,4-dinitrobenzene, resp.: MeNH2, 0.188, 0.152; EtNH2, 0.0518, 0.0496; PrNH2, 0.0535, 0.0530; BuNH2, 0.0571, 0.0553; AmNH2, 0.0583, 0.0567; C7H15NH2, 0.0615, 0.0608; Me2NH, 2.09; 2.10; Et2NH, 0.0108, 0.0117; Pr2NH, 0.00960, 0.01065; iso-PrNH2, 0.00666, 0.00637; sec-butylamine, 0.00548, 0.00540; iso-AmNH2, 0.0564, 0.0554; isohexylamine, 0.0607, 0.0587; (iso-Bu)2NH, 0.00396, 0.00415; (iso-Am)2NH, 0.0099, 0.0113; allylamine, 0.0263, 0.0262; benzylamine, 0.0271, 0.0278; piperidine, 1.148, 1.163; hydrazine, 0.358, 0.371. Therefore, the iso-amines react more slowly than the normal amines. Secondary amines react much more slowly than primary amines with the exception of Me2NH which reacts much more rapidly than MeNH2. The difference in the velocities between the Cl and Br derivs. is small and with the secondary amines examined the Br compound reacted more rapidly than the Cl compound In the reaction with Na alkylates, however, the Cl compound reacts much more quickly than the Br derivative (Lulofs, Rec. trav. chim. 20, 292(1901)). In all the cases investigated the reaction was shown to be a bimol. one. The reaction between the Cl compound and NH3 was measured at 100° in alc. of various strengths, sealed tubes being used; the following consts. were determined: 100% EtOH, 0.0384; 95.5%, 0.0365; 90.4%, 0.0333; 85.5%, 0.0324; 79.8%, 0.0364; 73.9%, 0.0338; for the Br compound in absolute EtOH the figure 0.0319 was determined It thus appears that the addition of water has a retarding influence on this reaction. The following compds. which are not recorded in the literature are described: 2,4-dinitroisobutylaniline, m. 56°; 2,4-dinitroisohexylaniline, m. 63°. Two new cases of dimorphism were discovered, with 2,4-dinitrodimethylaniline, m. 87° and 74°, and with 2,4-dinitrodiethylaniline, m. 80° and 69° (cf. van Alphen, C. A. 24, 2441; 26, 1272-3, 2447, 3789).
IT 837-64-9P, Aniline, N,N-diethyl-2,4-dinitro-
RL: PREP (Preparation)
(preparation of)
RN 837-64-9 CAPLUS

L4 ANSWER 309 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzenamine, N,N-diethyl-2,4-dinitro- (9CI) (CA INDEX NAME)



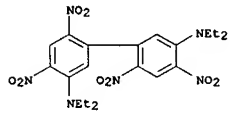
L4 ANSWER 310 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1932:23387 CAPLUS
DOCUMENT NUMBER: 26:23387
ORIGINAL REFERENCE NO.: 26:2447c-h
TITLE: Dimorphism of tetranitrobiphenyl derivatives. II
AUTHOR(S): van Alphen, J.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1932), 51, 361-8
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB cf. C. A. 26, 1272-3. Previously it has been shown (C. A. 24, 2441) that the dimorphous 2,4-dinitroanisole gives dimorphous tetranitro derivs. in which both the nuclei are bound in the o-position to the OMe groups. The present paper deals with tetranitrobiphenyl compds. derived from the same parent compound, the nuclei being, however, bound in the m-position to the OMe groups. 4,4',6,6'-Tetranitro-3,3'-dimethoxybiphenyl was prepared from 3,4,6-MeO(O2N)2C6H2Cl (cf. Blanksma, Rec. trav. chim. 21,321(1902)) by heating with an equal weight of Cu bronze at 235°; at 240° a violent reaction frequently occurs, but the yield is small. Therefore this compound was prepared from (3-ClC6H4)2 (cf. Ullmann, Ann. 332, 54(1904)) which was first nitrated with HNO3H2SO4 on the water bath to 4,4',6,6'-tetranitro-3,3'-dichlorobiphenyl, which was obtained in 2 forms, m. 184° and 191°, the latter modification being obtained on keeping the molten compound for some time at 170°. On cooling down the AcOH solution the compound m. 184° was obtained but the addition of boiling water gave the compound m. 191° together with that m. 184°. On the other hand, the addition of water to the acetone solution gives the pure compound m. 191°, while the lower-melting form is obtained on the addition of EtOH. The action of NaOMe in boiling MeOH converts the Cl compound into the corresponding MeO derivative, mentioned above, which, however, could be obtained in 1 form only, m. 244°. The di-EtO derivative prepared in an analogous way, was obtained in 2 forms, m. 198° and 208°; on throwing the powdered crystals, on a block heated to 194°, they melt but then solidify immediately and m. again 208°. On introducing the crystals, in a narrow glass tube, into a bath at 198°, they do not melt, however, the coarser fragments only becoming dull and the sharp edges being rounded. The corresponding amino compound, obtained in the usual way from the di-Cl compound, m. 297°, does not show dimorphism, nor does the di-NHMe compound, which does not m. 360°, but explodes at a higher temperature The latter compound, on nitration, affords 4,4',6,6'-tetranitro-3,3'-bis(methylnitramino)biphenyl, m. 210°, which is soluble only in acetone and does not show dimorphism. With boiling phenol the NMeNO groups are reconverted into the NHMe groups (cf. Van Romburgh, Rec. trav. chim. 5, 241(1886)) but the compound does not give the Liebermann or Thiele-Lachmann reactions for nitramines, the Bamberger-Franchimont test being positive, however. No dimorphism could be detected with the following compds.: 4,4',6,6'-tetranitro-3,3'-bis(ethylamino)biphenyl, m.

L4 ANSWER 310 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
315-20° (decompn.); 4,4',6,6'-tetranitro-3,3'-bis(dimethylamino)biphenyl, m. 270° and explodes at a somewhat higher temp.; 4,4',-6,6'-tetranitro-3,3'-bis(phenylamino)biphenyl, m. 278°. 4,4',6,6'-Tetranitro-3,3'-bis(diethylamino)biphenyl, however, shows dimorphism; on detg. the m. p. in the usual way, it m. 210°, but when thrown on a block, heated to 200°, it melts for a moment, solidifies again and then m. 210°.

IT 860589-48-6P, m,m'-Bianiline, N,N,N',N'-tetraethyl-4,4',6,6'-tetranitro-
RL: PREP (Preparation)
(preparation of)

RN 860589-48-6 CAPLUS
CN m,m'-Bianiline, N,N,N',N'-tetraethyl-4,4',6,6'-tetranitro- (3CI) (CA INDEX NAME)

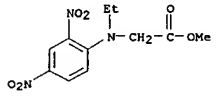


L4 ANSWER 311 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1932:8836 CAPLUS
DOCUMENT NUMBER: 26:8836
ORIGINAL REFERENCE NO.: 26:989c-e
TITLE: Synthesis of 1-ethyl-3-keto-1,2,3,4-tetrahydroquinoxaline
AUTHOR(S): van Romburgh, P.; Deys, W. B.
SOURCE: Proc. Acad. Sci. Amsterdam (1931), 34, 1004-6
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB The products formed by the action of Ac2O and ZnCl2 on dinitro derivs. of PhNEt2 were considered as derivs. of tetrahydroquinoxaline and were represented as nitrated 1-ethyl-3-keto-1,2,3,4- tetrahydroquinoxaline (I) (C. A. 21, 382). The ester 2,4-(NO2)2C6H3NEtCH2CO2Me (II) was synthesized by the action of HNO3 on PhNEtCH2CO2Me prepared from Ph- NHEt by heating with ClCH2CO2Me. Reduction of II with NH4OH gave a brown amorphous substance from which no definite product could be isolated. The ethylation of 3-ketotetrahydroquinoxaline by heating in a sealed tube as 100° for 2 hrs. with EtI gave 1-ethyl-3-ketotetrahydroquinoxaline (III), m. 98-9°. The reaction product (I) from 2,4-(NO2)2C6H3NEt2 with ZnCl2 and Ac2O was reduced with Fe and HCl and was isolated as the HCl salt. Treatment with H2SO4 and NaNO2 in alc. at 0° gave on neutralization a product identical with III. It is concluded that the formula of I was correctly assigned.

IT 857794-62-8P, Glycine, N-(2,4-dinitrophenyl)-N-ethyl-, methyl ester
RL: PREP (Preparation)
(preparation of)

RN 857794-62-8 CAPLUS
CN Glycine, N-(2,4-dinitrophenyl)-N-ethyl-, methyl ester (3CI) (CA INDEX NAME)



L4 ANSWER 312 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1932:6115 CAPLUS
DOCUMENT NUMBER: 26:6115
ORIGINAL REFERENCE NO.: 26:707g-i,708a-h
TITLE: Nitrosoresorcinol and the oxime of tetraketocyclohexene corresponding to it
AUTHOR(S): Borsche, W.; Weber, H.
SOURCE: Ann. (1931), 489, 270-95
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

GI For diagram(s), see printed CA Issue.

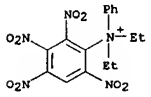
AB This work was undertaken in an effort to prepare 1,2,3,4-C6H2(NO2)4, previously studied by Nietzki and Geese (Ber. 32, 505(1899)). Dinitrosoresorcinol (I), best crystallized by adding 2-3 cc. H2O to 3 g. in 30 cc. MeOH, crystallizes with 1 mol. H2O. Trioximinoketocyclohexene (II) may be obtained from I and NH2OH in acid or alkaline solution, both ways giving a mixture of the 2 isomers (IIa) and (IIb), in which IIa predominates; the acid method gives a II which is more easily filtered; in the calculated amount of 4 N NaOH the tri-Na salt seps. as dark red crystals; CO2 gives the Na salt, red needles, both crystallizing with 1 mol. H2O. I (37.2 g.) and 42 g. NH2OH.HCl in 900 cc. MeOH and 300 cc. concentrated HCl, heated 3 days on the H2O bath, give 37 g. of tetraoximinocyclohexene (III), crystallizing with 1 mol. H2O, decomps. 210°. Nitrosoresorcinol (6 g.) and 15 cc. AC2O give diacetylhydroxyquinone monoxime, m. 120°; it decomps. on standing; di-Bz derivative, m. 150-1°. I and Ac2O, warmed 5 min. on the H2O bath, give diacetyldioximinodiketocyclohexene, yellow, m. 119-20°; di-Bz derivative, m. 182-4°. II and Ac2O give a tri-Ac derivative, m. unsharply between 118-139°; this is very unstable and on warming with MeOH gives a mixture of the 2 acetylbenzofurazanquinone monoximes (IV); fractional crystallization from C6H6 gives the pure IVa, light yellow, m. 142-3° (decomposition); with very dilute MeOH-HCl there results 4,7-benzofurazanquinone monoxime, m.172°; Bz derivative, light brown, m. 184°. III and Ac2O several days at 0° and then a day at room temperature, give the tetra-Ac derivative, m. 178-9°; boiling III with Ac2O 0.5 hr. gives the di-Ac derivative, m. 175°, of 4,7-benzofurazanquinone dioxime (V), brown, m. 225-6°. Crude IV and NH2OH in MeOH-HCl give a mixture of the 2 V, of which Va is diacetylated by Ac2O, while Vb is dehydrated to benzodifurazan (VI), light yellow, m. 62°, which is remarkably stable toward hot HNO2 and may be crystallized therefrom. VI results by heating Vb with Ac2O and not by saponification of the di-Ac derivative with NaOH. Catalytic reduction of V in MeOH gives 4,7-diaminobenzofurazan (VIIa), red, m. 193-4°; di-Ac derivative, yellow, decomps. 320°. VI gives 4,5-diaminobenzofurazan (VIIb), dark yellow, m. 151°; di-Ac derivative, yellow, m. 217-8°; with MeOH and HCl there results 2-methyl-4,5-furazanobenzimidozole (VIII), m. 285° (decomposition); reduction of the mixture of Va and Vb gives a mixture of VIIa and VIIb. Oxidation of 4 g. of the mixture of IV with 12 g. HNO3 (d. 1.30) and 4 g. HNO3 (d. 1.39) 6 hrs. at 0°, 12 hrs. at room temperature and 3 hrs. at 50° gives 4,6-dinitro-7-hydroxybenzofurazan, m.

L4 ANSWER 312 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
156° (decompn.); K salt; pyridine salt, yellow, m. 182-4°; diethylaniline salt, yellow, m. 158°. Oxidation of II with HNO3 gives 4,6-dinitro-7-hydroxybenzofuroxan, m. 132-3°; K salt; the HO group could not be replaced by Cl; pyridine salt, yellow-red, m. 215°; diethylaniline salt, yellow, m. 176°. Oxidation of III gives 4,7-dinitrobenzofuroxan, yellow, m. 170-2°. 2,3,4,6-C6H(NO2)4OH with PhNEt2 and p-MeC6H4SO2Cl gives diethylphenyltetranitro-phenylammonium chloride, yellow, m. 125-6°; C5H5N gives only the pyridine salt, yellow, decomps. 310°, explodes on quick heating. Nitrosoresorcinol. and 2,4-(O2N)2-C6H3NHNH2 in MeOH-HCl
give hydroxyquinone oxime 2,4-dinitrophenylhydrazone, red-brown, m. 205°; HNO3 in AcOH gives 2,4,2',4'-tetranitro-5-hydroxyazobenzene, yellow, m. 228-9°. I and o-O2NC6H4NHNH2.HCl in AcOH give the bis(2-nitrophenylhydrazone) of oximinotriketocyclohexene, red-brown crystals with 1 mol. H2O, m. 273°; oxidation with HNO3 gives 2,6(?)-bis(2-nitrobenzeneazo)-3-nitrophenol (IX), reddish yellow, m. 264° (decompn.). The bis(4-nitrophenylhydrazone), red, crystg. with 1 mol. H2O, m. 272°; oxidation gives the 4-NO2 deriv. of IX, reddish yellow, m. 325°. The bis(2,4-dinitrophenylhydrazone) of dioximinodiketocyclohexene, from I and 2,4-(O2N)2C6H3NHNH2, red, m. 266°; oxidation gives the 2,4-di-NO2 deriv. of IX, red, m. 172°. II gives a 2-nitrophenylhydrazone, red, m. 210-1°; oxidation gives a nitro(nitrobenzeneazo)benzo-furazan, yellow, m. 197-8°; the 4-nitrophenylhydrazone, red, m. 220-2°; the oxidation product is yellow-red and m. 243-4°; the 2,4-dinitrophenylhydrazone, red, m. 226°; the oxidation product, yellow, m. 192° and 212°.

IT 860583-84-2P, Ammonium, diethylphenyl-2,3,4,6-tetranitrophenyl-, chloride
RL: PREP (Preparation)
(preparation of)

RN 860583-84-2 CAPLUS

CN Ammonium, diethylphenyl-2,3,4,6-tetranitrophenyl-, chloride (3CI) (CA INDEX NAME)



● Cl-

L4 ANSWER 313 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1928:11297 CAPLUS
DOCUMENT NUMBER: 22:11297
ORIGINAL REFERENCE NO.: 22:1350i,1351a-g
TITLE: Replacement of the halogen atom or the alkoxy group in
1-chloro-, 1-methoxy- or 1-ethoxy-2,4-dinitro- and 2,4,5-trinitronaphthalenes by various other groups
AUTHOR(S): Talen, H. W.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1928), 47, 346-62
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.

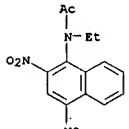
AB 1-Chloro-2,4-dinitronaphthalene (I) was prepared according to the method of
Ullmann and Bruck (C. A. 2, 2697; 3, 435) by the action of p-MeC6H4SO2Cl and PhNEt2 on 1,2,4-C10H5(OH)(NO2)2; from the Cl-compound the MeO and EtO derivs. were obtained by the action of NaOMe and NaOEt. The products described below were all prepared in the same way, viz., by heating one g.
of the Cl or alkoxy compound with twice the calculated amount of the amine in 25
cc. absolute alc. at 100° in a sealed tube for several (at most 5) hrs. The products form beautifully crystalline, yellow to orange substances, well
suited for the identification of amines; for solubility data the original paper
must be consulted. 2,4-Dinitronaphthalenes: 1-amino, m. 242°; 1-methylamino, existing in 2 modifications which could not be converted into one another, orange, m. 167.5°, and yellow, m. 179-80°; 1-ethylamino, m. 172°; 1-ethylacetylamino, m. 86-7°, obtained by adding a drop of concentrated H2SO4 to the EtNH compound in Ac2O;
1-propylamino, m. 129°; 1-butylamino, m. 89°; 1-amylamino, m. 74°; heating for 15 hrs. at 100° being necessary in order to obtain a Cl-free product; 1-heptylamino, m. 58°; 1-acetylamino, obtained on boiling 0.5 g. of the amino derivative in 10 cc. Ac2O during a
min., then adding one drop of concentrated H2SO4 and allowing the solution to stand
overnight. On recrystg. this substance from AcOH, beautiful parallelogram-like platelets, m. 117° and containing 1 mol. AcOH of crystallization, were obtained; at 150° the AcOH is given off and the AcOH-free substance, m. 258-9°, obtained. This substance dissolves in moderately dilute caustic alkali with an orange-red color, on acidification the unchanged yellow Ac compound being obtained again; it is
therefore assumed that the alkaline solution contains the quinoid form, CH:CH.C .
C(:NAc). CNO2. On adding 0.88 g. H2NCONHNH2.HCl in 10 cc. water, 20 cc. alc. and 15.85 cc. 0.5 N alc. NaOEt to 1 g. I in 100 cc. alc., boiling for
10 min. and letting stand overnight, 2,4-dinitronaphthyl-1-semicarbazide, decomposing explosively at 185-7°, is obtained. When 1 g. I is heated

L4 ANSWER 313 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
in a sealed tube with 0.83 g. semioxamazide and 30 cc. alc. for 10 hrs. at
100°, 2,4-dinitronaphthyl-1-semioxamazide, decompg. explosively at 227-8°, is formed. On nitration of I the chief product consists of 1-chloro-2,4,5-trinitronaphthalene, m. 147-8°, impure 1,2,4,8-C10H4Cl(NO2)3 being obtained as a by-product. On treating 1,2,4,5-C10H4Cl(NO2)3 with NaOMe and NaOEt, it is rapidly converted into 1-methoxy-2,4,5-trinitronaphthalene, m. 153° and the 1-EtO homolog, m. 151° (cf. following abstr.), which could be prepd. also on adding 2 g. 1-C10H7OMe or 1-C10H7OEt drop by drop to 14 cc. abs. HNO3, cooled to -10° letting stand for an hr. at room temp., pouring on to finely crushed ice and recrystg. the ppt. from AcOEt. From 1-chloro- and 1-alkoxy-2,4,5-trinitronaphthalene the following derivs. were prepd. in the same way as described above for I. 2,4,5-Trinitronaphthalenes: 1-amino, m. 310°; 1-acetylamino, m. 275°, passing in alk. soln. into the quinoid form; 1-methylamino, m. 206°; 1-ethylamino, m. 160°; 1-propylamino, m. 139°; 1-butylamino, m. 121°; 1-amylamino, m. 144-5°; 1-heptylamino, m. 99.5-100.5°; 2,4,5-trinitronaphthyl-1-semicarbazide, exploding at 173°; 1-semioxamazide, exploding at 236°. The same regularities in the course of the m. ps., noticed previously by van der Kam for the derivs. of primary amines with a normal C chain and 2,1,6,8-C10H4Cl(NO2)3 and 2,4-(O2N)2C6H3Cl (C. A. 21, 2883) make their appearance also in the m. ps. of the derivs. of these primary amines and I
and 1,2,4,5-C10H4Cl(NO2)3.

IT 860746-70-9P, Acetamide, N-(2,4-dinitro-1-naphthyl)-N-ethyl-
RL: PREP (Preparation)
(preparation of)

RN 860746-70-9 CAPLUS

CN Acetamide, N-(2,4-dinitro-1-naphthyl)-N-ethyl- (3CI) (CA INDEX NAME)

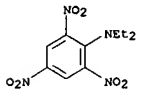


L4 ANSWER 314 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1927:5989 CAPLUS
DOCUMENT NUMBER: 21:5989
ORIGINAL REFERENCE NO.: 21:740a-e
TITLE: Some physical properties of nitro derivatives
AUTHOR(S): Desvergnes, Louis
SOURCE: Moniteur Scientifique du Docteur Quesneville (1926), 16, 201-8
CODEN: MSDQAH
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

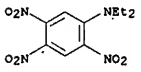
AB cf. C. A. 20, 2325. 2,4,6-Trinitrobenzoic acid, m. 228.7°, solubility (at 25° except with H2O), in H2O at 23.5° 2.053, at 50° 4.180, in boiling H2O decomps. into C6H3(NO2)3 and CO2, in EtOAc 21.053, Me2CO 22.122, 96% EtOH 27.534, absolute alc. 26.590, MeOH 50.601, C6H6 0.308, CHCl3 0.371, anhydrous Et2O 14.706, CS2 0.136, CCl4 0.070, C7H8 0.376; it dissolves in and reacts with C5H5N to give 1,3,5-C6H3(NO2)3 and picolinic acid. 2,4,6-Trinitromonoethylaniline, m. 81.5°, solidifies 81.2°, solubility (at 24° in all cases except H2O), in H2O at 19° 0.010, at 50° 0.031, at 100° 0.146, in EtOAc 40.668, Me2CO 123.996, 96% EtOH 0.812. absolute EtOH 1.114, MeOH 1.950, C6H6 107.962, CHCl3 74.693, anhydrous Et2O 2.568, C5H5N 125.469, CS2 0.942, CCl4 0.898, C7H8 64.180. 2,4,6-Trinitrodiethylaniline, m. 166.8°; solubility (at 20° in all cases except H2O), in H2O at 20° trace, at 50° 0.005, at 100° 0.020, in EtOAc 2.529, Me2CO 4.209, 96% alc. 0.051, absolute alc. 0.115, MeOH 0.150, C6H6 4.960, CHCl3 3.664, anhydrous Et2O 0.357, C5H5N 5.697, CS2 0.134, CCl4 0.194, C7H8 4.280. 2,4-Dinitrophenyl picrate, m. 210.2°, solubility in H2O at 27° (48 hrs.' contact) 0.007, at 50° (48 hrs.' contact) 0.017, at 100° (1 hr.'s contact)
0.095 (decomposition takes place proportionally to the time and temperature of
contact), EtOAc at 23° 6.704, at 50° 7.46, Me2CO at 23° 19.985, at 50° 36.08, 96% EtOH at 23° 0.449, at 50° (24 hrs.' contact) 1.25 (prolonging the contact to 48 hrs. gives 1.702, showing decomposition takes place), absolute alc. at 23° 0.588,
at 50° 0.91, C6H6 at 23° 0.530, at 50° 0.87, CHCl3 at 23° 0.226, at 50° 0.30, MeOH at 23° 1.682, at 50° 3.06 (here also decomposition takes place), anhydrous Et2O at 23° 0.256, C5H5N at 23° 45.41 (the solution is dark brown, and evaporation in vacuo gives a black pasty residue), CS2 at 23° 0.023, CCl4 at 23° 0.023, at 50° 0.06, C7H8 at 23° 0.667, at 50° 1.35. 2,4,6-Trinitrophenylethylnitroamine, m. 95.7°, solubility (at 25° and at 50° except in the case of H2O), in H2O at 22° 0.006, at 50° 0.026, at 100° 0.271 with
decomposition and formation of isopicric acid, EtOAc 50.688, 108.97, Me2CO
146.033, 339.98, 96% EtOH 1.151, 4.56, absolute alc. 1.627, 4.60, MeOH 4.202,
11.64, C6H6 19.770, 62.59, CHCl3 3.110, 12.58, anhydrous Et2O (at 25° only) 1.327, C5H5N 17.797, 258.92 with decomposition and formation of isopicric
acid, CS2 (at 25° only) 0.067; CCl4 0.051, 0.288, C7H8 11.948, 42.17. (The solubilities presumably are in g. of compound dissolved in 100
cc. of solvent, but this is specifically mentioned only with 2,4,6-(O2N)3C6H2NEt2).

IT 13029-07-7P, Aniline, N,N-diethyl-2,4,6-trinitro-
RL: PREP (Preparation)

L4 ANSWER 314 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN . (Continued)
(prepn. of)
RN 13029-07-7 CAPLUS
CN Benzenamine, N,N-diethyl-2,4,6-trinitro- (9CI) (CA INDEX NAME)

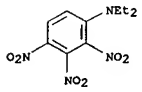


L4 ANSWER 315 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1925:7162 CAPLUS
DOCUMENT NUMBER: 19:7162
ORIGINAL REFERENCE NO.: 19:977i,978a-b
TITLE: Hydroferrocyanides and hydroferricyanides of the organic bases. IV
AUTHOR(S): Cumming, Wm. M.
SOURCE: Journal of the Chemical Society, Transactions (1924), 125, 2541-2
CODEN: JCHTA3; ISSN: 0368-1645
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 18, 2330. Organic bases in EtOH, treated with freshly prepared EtOH-H3Fe(CN)6, at -18° if necessary, precipitate salts containing in most cases EtOH of crystallization In the following, A stands for the base, B for H3Fe-(CN)6, C for EtOH: aniline, A3B,C, plates; o-toluidine, A3B,0.5C, lemon-yellow square plates; m-derivative, A3B,0.5C, light green plates; p-derivative, A3B,1.5C, green plates: o-phenylmediamine, A3B,2.5C, brown plates; m-derivative, A3B,1.5C, lemon-green plates; methylaniline, A3B, light green plates; dimethylaniline, A2B,C, light green plates; p-bromo-dimethylaniline, A2B,C, green, cubic prisms; p-nitrosodimethylaniline, A2B,C, red, amorphous; pyridine, A3B,0.5C, lemon-green needles; quinoline, A3B,0.5C, buff, amorphous; isoquinoline, A3B,0.5C, yellow, amorphous; β-naphthylamine, A3B,2C, grayish white plates; piperazine, A3B,C, green plates; piperidine, A3B,C, lemon-green needles; benzylamine, A3B,1.5C, silvery plates; hexamethylenetetramine, A3B,1.5C, green, amorphous; o-anisidine, A4B,2C, green needles; p-xylidine, A2B,3C, green plates; dimethylaminoazobenzene, A2B,2C, red plates; hydrazobenzene, A2B,4C, plates with a blue tinge; o-hdrazotoluene, plates. The following hydroferrocyanides (D) were precipitated in neutral solution: methylaniline, A3D, white plates; dimethylaniline, A2D,2C, plates; p-bromodimethylaniline, A2D,2C, needles; p-nitrosodimethylaniline, A4D,C, violet plates and A4D,7C, violet plates; o-dianisidine, A3D,4C, pale green plates.
IT 861525-95-3P, Aniline, N,N-diethyl-3,4,6-trinitro-
861793-42-2P, Aniline, N,N-diethyl-2,3,4-trinitro-
RL: PREP (Preparation)
(preparation of)
RN 861525-95-3 CAPLUS
CN Aniline, N,N-diethyl-2,4,5-trinitro- (1CI) (CA INDEX NAME)

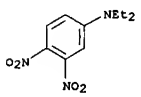


RN 861793-42-2 CAPLUS

L4 ANSWER 315 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Aniline, N,N-diethyl-2,3,4-trinitro- (2CI) (CA INDEX NAME)

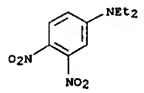


L4 ANSWER 316 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1924:399 CAPLUS
DOCUMENT NUMBER: 18:399
ORIGINAL REFERENCE NO.: 18:49f-h
TITLE: The action of ammonia and of amines on 3,4-dinitrodimethylaniline and 3,4-dinitrodiethylaniline
AUTHOR(S): van Romburgh, P.
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la Belgique (1923), 42, 804-7
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB In these 2 compds. the NO2 at position 3 is easily replaced by the amino or alkylamino group giving mononitro-m-phenylenediamine derivs., as was easily proved by converting them into trinitro-m-phenylenedialkylnitramines with fuming HNO3. 3,4-(O2N)2C6H3NMe2 (I) heated with NH4OH-EtOH for some hrs. at 120° in sealed tube gave 4-nitro-3-aminodimethylaniline, m. 135°. I heated at 125° with MeNH2 gave 4-nitro-3-methylaminodimethylaniline, m. 115°, which in H2SO4 (1:1) with NaNO2 gave 4-nitro-3-methylnitrosoaminodimethylaniline. I treated similarly with Me2NH gave 4-nitro-tetramethyl-m-phenylenediamine, m. 81°. With EtNH2 I gave 4-nitro-3-ethylaminodimethylaniline, m. 98°. Satisfactory results were not obtained with Et2NH. 4,3-O2N(H2N)C6H3NEt2 (III) with NH3 gave 4-nitro-3-aminodiethylaniline, m. 139°; with MeNH2, 4-nitro-3-methylaminodiethylaniline, m. 96-7°; with Me2NH, 4-nitro-3-dimethyl-aminodiethylaniline, m. 63-4°; with EtNH2, 4-nitro-3-ethylaminodiethylaniline. The action of Et2NH with III was very slow and gave unsatisfactory results.
IT 35998-97-1, Aniline, N,N-diethyl-3,4-dinitro-
(reaction with amines and with NH3)
RN 35998-97-1 CAPLUS
CN Benzenamine, N,N-diethyl-3,4-dinitro- (9CI) (CA INDEX NAME)

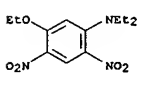


L4 ANSWER 317 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1924:398 CAPLUS
DOCUMENT NUMBER: 18:398
ORIGINAL REFERENCE NO.: 18:48i,49a-f
TITLE: Nitrosohydrazones. II
AUTHOR(S): Busch, M.; Schaffner, S.
SOURCE: Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen (1923), 56B, 1612-6
CODEN: BDCBAD; ISSN: 0365-9488
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 10, 1187. It was shown in the first paper that nitrosohydrazones are nitrosamines and that their conversion into nitroaldehyde hydrazones, RC(NO2):NNHR, is effected by a migration of the NO group from N to C. Furthermore, in the ketone nitrosohydrazones the NO group shows a similar tendency to take up O and change its position in the mol., forming a nucleus-substituted NO2 derivative Thus Ph2C:NN(NO)Ph on long standing in Et2O or C6H6 gives p-O2NC6H4NHN:CPh2 (I) instead of the expected PhN:NC(NO2)Ph2 (II), which Bamberger, Schmidt and Levinstein thought they had obtained in a different way (Ber. 33, 2055(1900)). A repetition of their work has shown that their product was really I: PhNH2 diazotized in HCl and poured into cold KOH was slowly added to MeNO2 in KOH, which produced much foaming and the deposition of a brown-red resinous mass; the alkaline filtrate with excess of CO2 yielded more of a red resin; the filtrate from this was acidified with cold dilute H2SO4 and extracted several times with Et2O and the exts. were shaken with concentrated NaOH, which gave an abundant precipitate of Ph2C:N(:O)ONa; this with 1 equivalent PhN2Cl in cold AcOH gave a thick light yellow oil whose alc. solution on short boiling deposited B., S. and L.'s compound, m. 154°, identical in all respects with I. It is believed that II is first formed from the Ph2C:NO2Na and PhN2Cl and is in fact the oily substance which first seps. and that it is during the treatment with boiling alc. that it rearranges into I. A number of other ketone hydrazones have been nitrosated to study the effect of nucleus substitution in the PhNHNH2 residue both on the course of the nitrosamine formation and on the oxidation and rearrangement of the latter into the NO2 hydrazones. It had already been noted that in the formation of I there are also formed small amts. of the o-NO2 and even of the o,p-(O2N)2 derivs. It has now been found in a few cases that the nitrosation proceeds smoothly but that the rearrangement is much hindered when the p-position is occupied and completely prevented when both the p-and one of the o-positions are occupied. Benzophenone p-tolylhydrazone (17 g. from 9 g. p-MeC6H4NHNH2 and 13.4 g. Ph2CO boiled 2 hrs. in 50 cc. alc. and 1 cc. AcOH), yellowish, m. 88°, gives almost quant. in AcOH with concentrated aqueous NaNO2 the nitrosamine, lemon-yellow, turns brown about 98°, begins to soften above 100° (evolution of nitrous

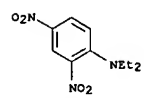
L4 ANSWER 317 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
gases), m. 108°, gives the Liebermann reaction; a suspension of the NO compd. in Et2O and a few drops AcOH allowed to stand several days at room temp. gives benzophenone o-nitro-p-tolylhydrazone, light red, m. 164°; the reaction is only about 60% complete after 6 days, and even in Et2O-alc. HCl a considerable amt. of the NO compd. still remains unchanged after 3 days. Benzophenone aminotolylhydrazone, from the NO2 compd. in AcOH suspension at 5° with Zn dust, yellow, m. 202°. Benzophenone o-tolylhydrazone, yellowish, m. 102°; nitrosation gives a non-homogeneous product from which on repeated crystn. are obtained straw-yellow columns, m. 176°, which give no Liebermann reaction and are undoubtedly the p-nitro-o-tolylhydrazone. Benzophenone asym-m-xylylhydrazone, faintly yellow, m. 84°; nitrosamine, orange-yellow, m. 104°, gives after several days in C6H6 benzophenone N-nitrosonitroxylyhydrazone, 2,4,6-Me2(O2N)C6H2N(NO)N:CPh2, blood-red, m. 119-20° (foaming).
IT 35998-97-1, Aniline, N,N-diethyl-3,4-dinitro-
(reaction with amines and with NH3)
RN 35998-97-1 CAPLUS
CN Benzenamine, N,N-diethyl-3,4-dinitro- (9CI) (CA INDEX NAME)



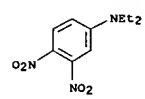
L4 ANSWER 318 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1915:19477 CAPLUS
DOCUMENT NUMBER: 9:19477
ORIGINAL REFERENCE NO.: 9:3223d-f
TITLE: Nitration of diethyl-m-phenetidine
AUTHOR(S): Reverdin, Frederic
SOURCE: Bull. soc. chim. (1915), 17, 278-82
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 9, 2228. Diethyl-m-phenetidine (A), m-EtC6H4NEt2, b. 286°, was formed by the interaction of m-EtOC6H4NH2 and EtBr. The 4,6-dinitro derivative (B) of (A), 3,4,6-(Et2N)(O2N)2C6H2OEt, yellow needles or prisms, m. 94°, was obtained by treating (A) in ice-cold glacial AcOH with HNO3 (d. 1.52). Further nitration of (B) in Ac2O with HNO3 (d. 1.52) yielded 4,6-dinitro-3-ethylnitramino-I-ethoxybenzene (C), needles from ligroin, m. 112°. If HNO3 (d. 1.4) and (A) are allowed to interact, 4,6-dinitro-3-monoethylamino-I-ethoxybenzene (D), yellow needles, m. 134°, is formed together with a compound, m. 75°, isolated from the mother liquors of (D), probably a NO derivative Alc. KOH acting upon (C) gave rise to 4,6-dinitro-3-ethylamino-I-phenol, yellow needles, m. 128-9°, isolated by means of its barium derivative, fine needles.
IT 860767-86-8P, m-Phenetidine, N,N-diethyl-4,6-dinitro-
RL: PREP (Preparation)
(preparation of)
RN 860767-86-8 CAPLUS
CN m-Phenetidine, N,N-diethyl-4,6-dinitro- (1CI) (CA INDEX NAME)



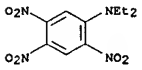
L4 ANSWER 319 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1911:7078 CAPLUS
DOCUMENT NUMBER: 5:7078
ORIGINAL REFERENCE NO.: 5:1281c-f
TITLE: Nitration of Diethylaniline
AUTHOR(S): Van Romburgh, P.
CORPORATE SOURCE: Org.-chem. Univ. Lab. Utrecht
SOURCE: K. Akad. Wetenschappen (1911), 18, 175-81
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB through Chemical Zentr., 1910, I, 1242. Diethylaniline dissolved in concentrate H2SO4, cooled to 0° and added, without allowing the temperature to rise above 5°, to a mixture of 1 pt. (by weight) of HNO3 to 3 pts. H2SO4 yields, on allowing to stand for some hrs. and then pouring into H2O containing ice, 3,4-dinitrodiethylaniline, Et2NC6H3(NO2)3, orange-colored precipitate, m. 95°. By the addition of H2O, 2,4-dinitrodiethylaniline, yellow crystals, m. 80° is precipitated NaOH causes precipitation of 3,6-dinitrodiethylaniline, red, m. 76°. 3,4-Dinitrodiethylaniline exists in an orange-colored, stable α-modification and in a yellow unstable β-modification, the former being obtained by slowly cooling, the latter, by rapidly cooling a b. concentrate solution By mixing the b. alc. solns., 3,4-dinitrodiethylaniline unites with 2,4-dinitrodiethylaniline forming a product containing 1 mol. of each of the constituent compds. Treatment with concentrate HNO3 converts 3,4-dinitrodiethylaniline into 3,4,6-trinitrodiethylaniline, Et2NC6H2(NO2)3, yellow crystals, m. 158°. By the action of Me2NH, it passes into 4,6-dinitro-3-dimethylaminodiethylaniline, Et2NC6H2(NO2)2NMe2, m.83°. This last compound is also obtained by treating 3,4,6-trinitrodimethylaniline, Me2NC6H2(NO2)3, m. 195°, with Et2NH.
IT 837-64-9P, Aniline, N,N-diethyl-2,4-dinitro- 35998-97-1P , Aniline, N,N-diethyl-3,4-dinitro- 861525-95-3P, Aniline, N,N-diethyl-2,4,5-trinitro-
RL: PREP (Preparation)
(preparation of)
RN 837-64-9 CAPLUS
CN Benzenamine, N,N-diethyl-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 35998-97-1 CAPLUS
CN Benzenamine, N,N-diethyl-3,4-dinitro- (9CI) (CA INDEX NAME)



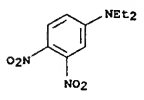
L4 ANSWER 319 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 861525-95-3 CAPLUS
CN Aniline, N,N-diethyl-2,4,5-trinitro- (1CI) (CA INDEX NAME)



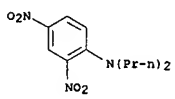
L4 ANSWER 320 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1910:14723 CAPLUS
DOCUMENT NUMBER: 4:14723
ORIGINAL REFERENCE NO.: 4:2649i,2650a-i,2651a-f
TITLE: Chromisomerism and Homochromisomerism of Nitroanilines
AUTHOR(S): Hantzsch, A.
SOURCE: Berichte der Deutschen Chemischen Gesellschaft (1910),
43, 1662-85
CODEN: BDCGAS; ISSN: 0365-9496
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. preceding and following abstrs. 4-Nitrotolyl-2-methylamine, O2NC6H3MeNHMe, is known to exist in both a yellow and an orange form, each of which m. 107-5°. An orange (red) form of the corresponding ethylamine has been described, but the author could only obtain a yellow modification, both m. 81°. Compds. of the type O2NC6H4NRR7 appear to occur in 1 form only. A substance, which is stated to be "1-nitro-,3,5-dinitrobenzene, C6H7O2N3 and is said to be produced by the action of aqueous (not alc.) (NH4)2S on "ordinary" trinitrotoluene, or on 3,5-dinitroaniline, was obtained as a brick-red solid, m. 139°. [It is evident that this portion of the original paper is quite erroneous. J. B. T.] The following derivs. of dinitrotoluidine, [Me: NRR1:NO2:NO2 = 4:1:2:6], have been investigated, for the sake of brevity only the names of the groups R or R1 are mentioned. Dipropyl-, m. 80°; Phenyl- and p-tolyl- are all yellow, but the last 2 are so only at ~60°. The following compds. range in color from light orange to brick-red, the intensity of color increases in the order named: dimethyl-, m. 50°; methyl-p-tolyl-, m. 146°; propyl-, m. 55°; phenyl- (at the ordinary temperature), m. 170°; p-tolyl- (at the ordinary temperature), m. 161°; methylphenyl-, m. 168°; ethyl-, m. 127°; o-tolyl-, m. 124°; methyl-, m. 126°. The following are dark red: m-tolyl-, m. 127°; methyl-o-tolyl-, m. 114°; α-naphthyl-, m. 94°; β-naphthyl-, m. 190°. Dimethyl-3,4-dinitroaniline, from dimethylaniline and HNO3 (d. 1.30), could only be obtained in yellow needles, m. 175°. Diethyl-3,4-dinitroaniline is prepared from diethylaniline, cone. H2SO4 and HNO3 (d. 1.52) and is separated from the 2,4-isomer by its smaller soluble in CHCl3 + petroleum ether. It exists in a stable, dark orange form, m. 95°, and in a labile, yellow modification, which is obtained from CHCl3 on the addition of petroleum ether. It is stable at the ordinary temperature when dry, otherwise it quickly passes to the orange form. The derivs. of 2,4-dinitroaniline could be obtained in 1 form only. Dipropyl-2,4-dinitroaniline, from Pr2NH and 2,4-dinitrochlorobenzene; m. 41°. Like the di-Me and di-Et derivs., it is yellow. m-Tolyl- and also p-tolyl-2,4-dinitroaniline are scarlet-red, m. 159° and 131°, resp. Methylphenyl-2,4,dinitroaniline, m. 165°; at the ordinary temperature it is reddish orange, at ~80° yellow, and above 140° intensely red. Ethyl-phenyl-2,4-dinitroaniline, m. 95°, behaves in a similar manner. o-Tolyl-2,4-dinitroaniline,

L4 ANSWER 320 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
MeC6H4NHC6H3(NO2)2, exists in 4 forms as follows: (a) Stable yellow form, from a saturated alc. soln. of any form by rapid cooling, thick, monoclinic prisms which are stable in contact with the mother liquor, m. 128-9° to an orange liquid which, however, when cooled and heated again remelts 128-9°. It is the most stable variety. (b) Labile, yellow form, m. 120-1°, is the least stable, it is obtained usually by cooling a cone. acetone soln. of (a) in a mixture of Et2O + CO2, by adding petroleum ether to the acetone soln. at -5°, by adding acetonitrile to (a), or by cooling to -75° a soln. of (a) in acetonitrile. Under similar conditions it is prepared more easily from (d). At its m. p. it passes quickly to (a). (c) Stable, orange forms produced by the slow cooling of a dil. alc. soln.; thin, reddish orange needles, m. 121°, passing then into (a). (d) Labile orange form deposited, together with (a), by the slow crystn. of a hot alc. soln., or, with greater certainty, by adding a little H2O, at the ordinary temp., to a soln. of (a) in glacial AcOH, or MeOH, At 110° it is transformed into (a) without m. The above substances do not differ in content of solvent of crystn.; in soln. all forms are orange and they are optically identical, at 130-40° an equilibrium mixture of orange and yellow forms is produced slowly. The effect on (c) and (d) of various solvents is described in detail, although in some cases (a) is obtained together with (c) and (d) from the resp. soln. of the orange forms, yet this production of (a) is regarded as being a secondary effect. The following derivs. of 2,4,6-trinitroaniline (picramide) have been examined; as before, the names refer to the groups represented by R of R1 in NRR1. Methyl, m. 111°; ethyl, m. 83°; are yellow and do not become brown in air, as stated by Romburgh. Dimethyl, yellow; when treated with HCl, at -70° and the salt exposed to air, it gives a very unstable orange form. Diethyl-, orange. Ethylisopropyl, yellow and orange. Phenyl-, m, 178°, reddish orange. Ethylphenyl-, dark red crystals, m. 108°. o-Tolyl-, orange crystals, m. 163°; in Et2O + CO2 it becomes yellow. m-Tolyl-, MeC6H4NHC6H2(NO2)3, exists in 3 forms: (a) Stable yellow, produced by adding petroleum ether to a fairly cone. soln. of any form in CHCl3; at 120° it becomes orange, and after cooling consists of (b). Slow evaporation of alc. or CHCl3 solns. of any form gives (b), the stable orange variety, hot soln. made from either (a) or (b) deposit mixtures of both forms; m. 130°. (c) Labile orange, is produced by cooling fused (a) or (b); m. 75°. It transforms spontaneously into (a); in presence of solvents it gives both (a) and (b). p-Tolylpicramide gives dark red crystals in addition to the yellow from, which is already known. The solns. are all orange. The orange modification is deposited from soln. of either isomer in CHCl3, CCl4, C6H6, or acetone. The red form is deposited alone from pyridine. Other solvents give mixtures. Both forms are stable when dry and m. 164°. Methyl-o-tolyl, reddish orange prisms, m. 164.5°. Methyl-p-tolyl, dark red prisms, m. 144-5°. Ethyl-p-tolyl, copper-red plates, m. 132°. p-Bromophenyl-, orange prisms, m. 180°. α-Naphthyl-, dark red prisms, m. 198°. β-Naphthyl- is stated by Bamberger to exist in a dark red and in an orange-yellow form, both m. 233°. The following figs. give the mol. wts. of the compds. mentioned, in the solvents indicated, the color of the soln. is also added; p-nitroaniline, in C6H6 (yellow) 136; o-nitroaniline, in hexane (yellowish) 137-42; in alc. (deep yellow) 138-44; dimethyl-3,4-dinitroaniline, in CHCl3 (yellow) 218-24; diethyl-3,4-dinitroaniline, in CHCl3 (orange) 245-50; dimethyl-2,4,6-trinitroaniline, in C6H6 (yellow) 247-54; diethyl-2,4,6-trinitroaniline, in C6H6 (reddish orange) 271-9; phenyl-2,4,6-trinitroaniline, in CHCl3

L4 ANSWER 320 OF 320 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(orange) 310-30; p-tolyl-2,4,6-trinitroaniline, in CHCl3 (orange) 306-11; in alc. (dark red) 334; methyl-p-tolyl-2,4,6-trinitroaniline, in CHCl3 (dark red) 345-53. These values show that in every instance the compd. was monomol. The following figures refer to the mol. ref., at 20°, for the D line: In CHCl3, dimethyl-2,4-dinitroaniline (yellow), 62.2; diethyl-2,4-dinitroaniline (yellow), 71.7; dipropyl-2,4-dinitroaniline (yellow), 81.1; in pyridine, dimethyl-3,4-dinitroaniline (yellow), 61.5; diethyl-3,4-dinitroaniline (orange), 69.3; in C6H6, dimethyl-2,4,6-trinitroaniline (yellow), 61.1; diethyl-2,4,6-trinitroaniline (orange), 71.2. The values for the first 3 compds. show that they all contain the same chromophore, whereas, in the case of the last 4 substances, the figures show that the yellow and orange chromophores are different in structure (p-, m- and o-quinoids). The ultraviolet absorption spectra of a number of the compds. described above have been determined in various solvents and the results plotted in the form of curves, which are reproduced in the original paper. Picryl chloride and Ph2NH form an additive product, orange crystals, m. 62°. When treated with CHCl3 + petroleum ether it is resolved into its constituents. Cf. following abstr.
IT 35998-97-1P, Aniline, N,N-diethyl-3,4-dinitro- 54718-72-8P , Aniline, 2,4-dinitro-N,N-dipropyl-
RL: PREP (Preparation)
(preparation of)
RN 35998-97-1 CAPLUS
CN Benzenamine, N,N-diethyl-3,4-dinitro- (9CI) (CA INDEX NAME)



RN 54718-72-8 CAPLUS
CN Benzenamine, 2,4-dinitro-N,N-dipropyl- (9CI) (CA INDEX NAME)



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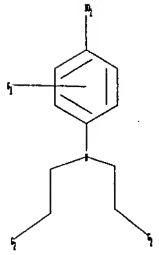

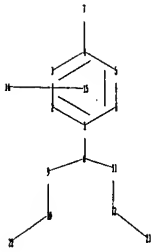

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4-7 9-10 11-12
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

G1:CN,SO2,NO2

G2:X,[*1]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:CLASS 14:CLASS 15:Atom 16:CLASS 17:CLASS 18:CLASS 19:CLASS
22:CLASS 23:CLASS

L5 STRUCTURE UPLOADED

=> d
L5 HAS NO ANSWERS
L5 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> l5
SAMPLE SEARCH INITIATED 09:51:02 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 55 TO ITERATE

100.0% PROCESSED 55 ITERATIONS 10 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 656 TO 1544
PROJECTED ANSWERS: 11 TO 389

L6 10 SEA SSS SAM L5

=> l5 full
FULL SEARCH INITIATED 09:51:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1058 TO ITERATE

100.0% PROCESSED 1058 ITERATIONS 188 ANSWERS
SEARCH TIME: 00.00.01

L7 188 SEA SSS FUL L5

=> file medline caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 172.10 464.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE ENTRY TOTAL SESSION
CA SUBSCRIBER PRICE 0.00 -15.60

FILE 'MEDLINE' ENTERED AT 09:51:12 ON 02 MAY 2007

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FILE 'CAPLUS' ENTERED AT 09:51:12 ON 02 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> l7
L8           58 L7

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9            47 DUP REM L8 (11 DUPLICATES REMOVED)

=> d ibib abs hitstr 1-47
```

L9 ANSWER 1 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:409493 CAPLUS
TITLE: Method for selectively depleting hypoxic cells within bone marrow, and cancer treatment method
INVENTOR(S): Pamar, Kalindi; Mauch, Peter; Down, Julian
PATENT ASSIGNEE(S): Genetix Pharmaceuticals, Inc., USA; Dana-Farber Cancer Institute, Inc.
SOURCE: PCT Int. Appl., 57pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007041546	A2	20070412	WO 2006-US38553	20060929

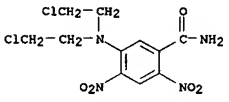
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-723183P P 20051003

AB The invention discloses an improved method for selectively depleting hypoxic cells within the bone marrow. The method can be used to enhance engraftment of hematopoietic stem cells (HSCs) in the bone marrow of a host subject. Also disclosed is a method for treating a cancer within the bone marrow of a host subject.

IT 142439-61-0, SN 23862
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for selectively depleting hypoxic cells within bone marrow, and cancer treatment method)

RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



L9 ANSWER 1 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

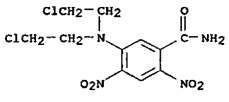
L9 ANSWER 2 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:472635 CAPLUS
DOCUMENT NUMBER: 145:356174
TITLE: Estimation of single-electron reduction potentials (E17) of nitroaromatic compounds according to the kinetics of their single-electron reduction by flavoenzymes
AUTHOR(S): Sarlauskas, Jonas; Nivinskas, Henrikas; Anusevicius, Zilvinas; Miseviciene, Lina; Maroziene, Audrone; Cenas, Narimantas
CORPORATE SOURCE: Institute of Biochemistry, Vilnius, LT-08662, Lithuania
SOURCE: Chemija (2006), 17(1), 31-37
CODEN: CHMJES; ISSN: 0235-7216
PUBLISHER: Lietuvos Mokslu Akademijos Leidykla
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because of the instability of nitroarom. anion-radicals, the single-electron reduction potentials of nitroarom. compds. are usually obtained by means of pulse-radiolysis and flash-photolysis. Here we present an alternative method of the estimation of single-electron reduction potentials of nitroarom. compds. at pH 7.0 (E17), based on the linear log rate constant vs. E17 dependences in their single-electron reduction by flavoenzymes electrontransferases. The geometric avs. of the bimol. steady-state rate consts. of the reduction of nitroaroms. by flavocytochrome b2, ferredoxin: NADP+ reductase, or NADPH: cytochrome P 450 reductase were used as the correlation parameters. The differences between the directly determined E17 for a number of nitroarom. compds. and their calculated values did not exceed 35 mV. This approach enabled us to characterize the E17 values of 36 previously uncharacterized nitroarom. compds., including important antitumor and antiparasitic agents and explosives.

IT 142439-61-0P
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); PRP (Properties); RCT (Reactant); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(estimation of single-electron reduction potentials (E17) of nitroarom. compds. according to kinetics of their single-electron reduction by flavoenzymes)

RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



L9 ANSWER 2 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

L9 ANSWER 3 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:472334 CAPLUS
DOCUMENT NUMBER: 143:19961
TITLE: Oncolytic ICP34.5-null herpes simplex virus expressing
E. coli nitroreductase for antitumor prodrug activation and cancer therapy enhancement
INVENTOR(S): Brown, Susanne Moira; Dunn, Paul
PATENT ASSIGNEE(S): Crusade Laboratories Limited, UK
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005049845	A2	20050602	WO 2004-GB4851	20041117
WO 2005049845	A3	20051027		
WO 2005049845	A9	20060817		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

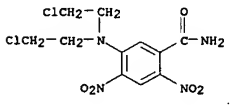
EP 1685254	A2	20060802	EP 2004-798569	20041117

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS

PRIORITY APPLN. INFO.:	GB 2003-26798	A 20031117
	WO 2004-GB4851	W 20041117

AB An herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding a nitroreductase (NTR) is disclosed. Disclosed herpes simplex viruses are indicated to be useful in the treatment of cancer which may involve gene directed enzyme prodrug therapy. In particular, the invention provides a novel second generation oncolytic mutant HSV, designated HSV1716/CMV-NTR/GFP (also called HSV1790). This mutant HSV is derived from oncolytic HSV strain 17 mutant 1716 (non-neurovirulent) and comprises the heterologous (i.e. non-HSV originating) E.coli nitroreductase protein coding sequence inserted at one or each ICP34.5 locus, disrupting the ICP34.5 protein coding sequence such that the ICP34.5 gene is nonfunctional and cannot express a functional ICP34.5 gene product. The generated HSV is capable of expressing the E.coli nitroreductase gene product under control of the inserted promoter.
HSV1790 can be used in gene directed enzyme-prodrug therapy (GDEPT) in

L9 ANSWER 3 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
combination with oncolytic HSV therapy and has shown significantly enhanced tumor cell killing in vitro and in vivo when used with the prodrug CB1954.
IT 142439-61-0, SN23862
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug, activated by recombinant nitroreductase; oncolytic ICP34.5-null herpes simplex virus expressing E. coli nitroreductase for antitumor prodrug activation and cancer therapy enhancement)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:409465 CAPLUS
DOCUMENT NUMBER: 142:463873
TITLE: Preparation of nitrophenyl mustard and aziridine alcohol prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents
INVENTOR(S): Denny, William Alexander; Atwell, Graham John; Yang, Shangjin; Wilson, William Robert; Patterson, Adam Vorn; Helsby, Nuala Ann
PATENT ASSIGNEE(S): Auckland Uniservices Limited, N. Z.
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005042471	A1	20050512	WO 2004-NZ275	20041029

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

NZ 529249	A	20060428	NZ 2003-529249	20031031
AU 2004285831	A1	20050512	AU 2004-285831	20041029
CA 2544335	A1	20050512	CA 2004-2544335	20041029
EP 1680394	A1	20060719	EP 2004-817434	20041029

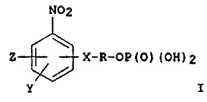
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

BR 2004016085	A	20070102	BR 2004-16085	20041029
CN 1902159	A	20070124	CN 2004-80039430	20041029
JP 2007509928	T	20070419	JP 2006-537921	20041029
US 2007032455	A1	20070208	US 2006-577078	20060713

PRIORITY APPLN. INFO.:	NZ 2003-529249	A 20031031
	NZ 2004-535618	A 20040928
	WO 2004-NZ275	W 20041029

OTHER SOURCE(S): MARPAT 142:463873
GI

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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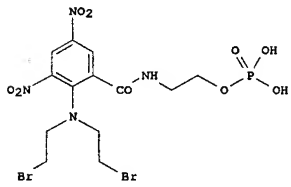
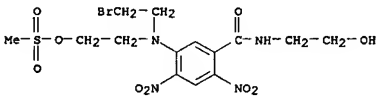


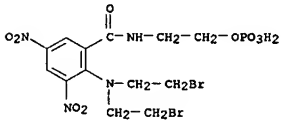
II

AB The present invention relates to novel nitrophenyl mustard and nitrophenylaziridine alcs., to their corresponding phosphates (shown as I; variables defined below; e.g. 2-[[2-[bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate (shown as II)), to their use as targeted cytotoxic agents; as bioreductive drugs in hypoxic tumors, and to their use in cell ablation, including gene-directed enzyme-prodrug therapy (GDEPT) and antibody-directed enzyme-prodrug therapy (ADEPT), in conjunction with nitroreductase enzymes. For I: X represents at any available ring position -CONH-, -SO2NH-, -O-, -CH2-, -NHCO- or -NHSO2-; R represents a lower C1-6 alkyl (un)substituted with ≥1 groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom; Y represents at any available ring position -N-aziridinyl, -N(CH2CH2W)2 or -N(CH2CHMeW)2, where each W = halogen or -OSO2Me; Z represents at any available ring position -NO2, -halogen, -CN, -CF3 or -SO2Me. Methods of preparation are claimed and 25 example prepns. of alcs. and 14 of phosphates are included. For example, 2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide was prepared in 3 steps (91, 100 and 95 %) starting with conversion of 2-chloro-3,5-dinitrobenzoic acid to 2-chloro-N-(2-hydroxyethyl)-3,5-dinitrobenzamide using SOCl2 and 2-aminoethanol, followed by reaction with N,N-bis(2-chloroethyl)amine hydrochloride to give 2-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide and then halide exchange with LiBr. The nitrophenyl mustard alc. was converted to II using di-tert-Bu diethylphosphoramidite/1H-tetrazole, then oxidation by 3-chloroperoxybenzoic acid (72 %) and acid hydrolysis (98 %).
IT 680199-01-3, 2-[N-(2-Bromoethyl)-5-[[(2-hydroxyethyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(phosphorylation; preparation of nitrophenyl mustard and aziridine alc.

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)
RN 680199-01-3 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

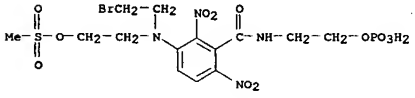


IT 851627-78-6P, 2-[[2-[Bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl hydrogen sodium phosphate 851627-79-7P,
2-[N-(2-Chloroethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate monosodium salt 851627-80-0P,
2-[N-(2-Bromoethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate monosodium salt 851627-81-1P,
2-[N-(2-Bromoethyl)-2,4-dinitro-3-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate monosodium salt
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pre-prodrug candidate; preparation of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)
RN 851627-78-6 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]-, monosodium salt (9CI) (CA INDEX NAME)



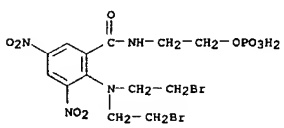
● Na

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



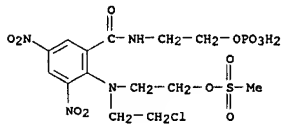
● Na

IT 851627-50-4P, 2-[[2-[Bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate 851627-58-2P,
2-[N-(2-Chloroethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-62-8P,
2-[N-(2-Bromoethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-72-0P,
2-[N-(2-Bromoethyl)-2,4-dinitro-3-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(pre-prodrug candidate; preparation of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)
RN 851627-50-4 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)



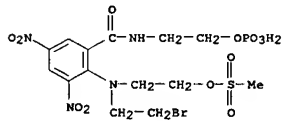
RN 851627-58-2 CAPLUS
CN Benzamide, 2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 851627-79-7 CAPLUS
CN Benzamide, 2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]-, monosodium salt (9CI) (CA INDEX NAME)



● Na

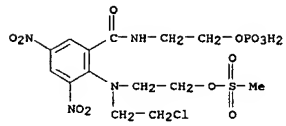
RN 851627-80-0 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]-, monosodium salt (9CI) (CA INDEX NAME)



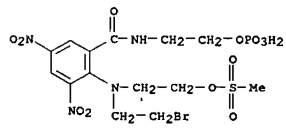
● Na

RN 851627-81-1 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-N-[2-(phosphonooxy)ethyl]-, monosodium salt (9CI) (CA INDEX NAME)

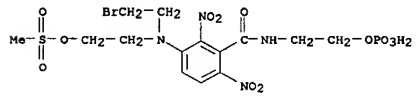
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-62-8 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)



RN 851627-72-0 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)

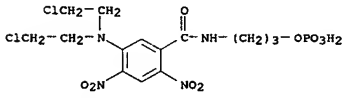


IT 851627-52-6P, 3-[[5-[Bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]propyl dihydrogen phosphate 851627-54-8P, 3-[[5-[Bis(2-bromoethyl)amino]-2,4-dinitrobenzoyl]amino]propyl dihydrogen phosphate 851627-56-0P, 2-[[2-[Bis(2-chloroethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate 851627-60-6P, 2-[[2-[Bis(2-bromopropyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate 851627-64-0P, 2-[[2-[Bis(2-iodoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate 851627-66-2P,
2-[N-(2-Iodoethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-68-4P, 2-[N-(2-Chloroethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-70-8P, 3-[[3-[Bis(2-bromoethyl)amino]-2,6-dinitrobenzoyl]amino]propyl dihydrogen phosphate 851627-74-2P,
2-[N-(2-Bromoethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-76-4P,

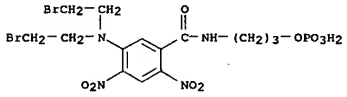
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

2-[N-(2-Iodoethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]carbonyl]anilino]ethyl methanesulfonate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pre-prodrug candidate; prepn. of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)

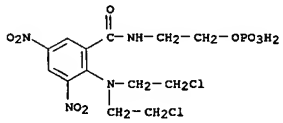
RN 851627-52-6 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)



RN 851627-54-8 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-2,4-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)

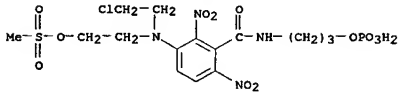


RN 851627-56-0 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)

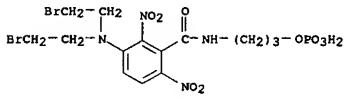


RN 851627-60-6 CAPLUS
CN Benzamide, 2-[bis(2-bromopropyl)amino]-3,5-dinitro-N-[2-

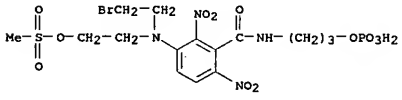
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



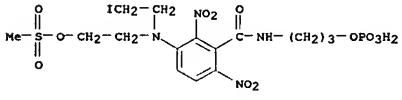
RN 851627-70-8 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-2,6-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)



RN 851627-74-2 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)

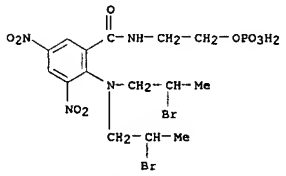


RN 851627-76-4 CAPLUS
CN Benzamide, 3-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)

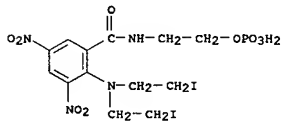


IT 150271-91-3, 5-[Bis(2-chloroethyl)amino]-2,4-dinitrobenzoic acid 680199-24-0, 5-[Bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitrobenzoic acid 680199-44-4, 2-[3-[[(2-Hydroxyethyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino]ethyl methanesulfonate 680199-47-7, 2-[3-[[(4-Hydroxybutyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino]ethyl methanesulfonate 851627-09-3, 5-[Bis(2-bromoethyl)amino]-2,4-dinitrobenzoic acid

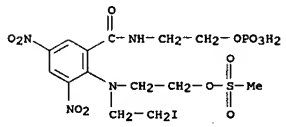
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)



RN 851627-64-0 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)



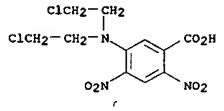
RN 851627-66-2 CAPLUS
CN Benzamide, 2-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-(phosphonooxy)ethyl]- (9CI) (CA INDEX NAME)



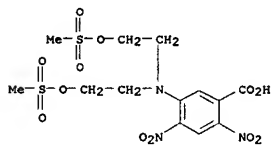
RN 851627-68-4 CAPLUS
CN Benzamide, 3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-N-[3-(phosphonooxy)propyl]- (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)

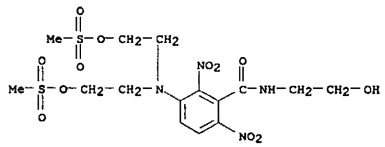
RN 150271-91-3 CAPLUS
CN Benzoic acid, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 680199-24-0 CAPLUS
CN Benzoic acid, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

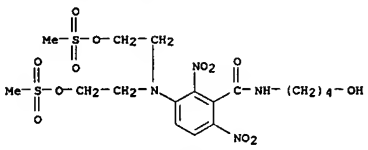


RN 680199-44-4 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

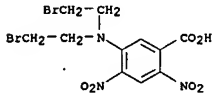


RN 680199-47-7 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(4-hydroxybutyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



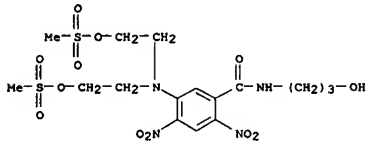
RN 851627-09-3 CAPLUS
CN Benzoic acid, 5-[bis(2-bromoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



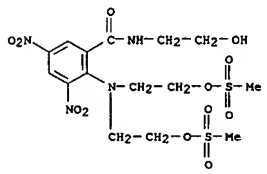
IT 680199-25-1P, 2-[5-[[(2-Hydroxyethyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino]ethyl methanesulfonate 680199-26-2P, 2-[5-[[(3-Hydroxypropyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino]ethyl methanesulfonate 680199-31-9P, 2-[2-[[(2-Hydroxyethyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-4,6-dinitroanilino]ethyl methanesulfonate 680199-46-6P, 2-[3-[[(3-Hydroxypropyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino]ethyl methanesulfonate 851627-16-2P, Methyl 5-[bis(2-bromoethyl)amino]-4-(methylsulfonyl)-2-nitrobenzoate 851627-17-3P, 5-[Bis(2-bromoethyl)amino]-4-(methylsulfonyl)-2-nitrobenzoic acid 851627-36-6P, 1-Methyl-2-[N-[2-[(methylsulfonyl)oxy]propyl]-2,4-dinitro-6-[[[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-37-7P, 2-[2-[[(2-Hydroxyethyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]propyl]-4,6-dinitroanilino]-1-methylethyl methanesulfonate 851627-41-3P, 2-[N-[2-[(Methylsulfonyl)oxy]ethyl]-2,4-dinitro-6-[[[3-[(tetrahydro-2H-pyran-2-yl)oxy]propyl]amino]carbonyl]anilino]ethyl methanesulfonate 851627-42-4P, 2-[2-[[(3-Hydroxypropyl)amino]carbonyl]-N-[2-[(methylsulfonyl)oxy]ethyl]-4,6-dinitroanilino]ethyl methanesulfonate 851627-51-5P, Di-tert-butyl 2-[[2-[bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl phosphate 851627-53-7P, Di-tert-butyl 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]propyl phosphate 851627-55-9P, Di-tert-butyl 3-[[5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzoyl]amino]propyl phosphate 851627-57-1P, Di-tert-butyl 2-[[2-[bis(2-chloroethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl phosphate 851627-59-3P,

2-[N-(2-Chloroethyl)-2-(6-tert-butoxy-8,8-dimethyl-6-oxido-5,7-dioxa-2-aza-

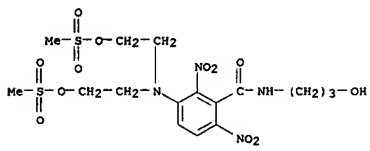
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-31-9 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 680199-46-6 CAPLUS
CN Benzamide,
3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

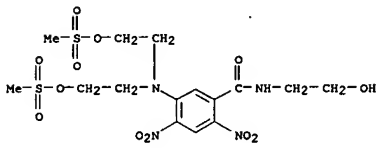


RN 851627-16-2 CAPLUS
CN Benzoic acid, 5-[bis(2-bromoethyl)amino]-4-(methylsulfonyl)-2-nitro-, methyl ester (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
6-phosphanonanoyl)-4,6-dinitroanilino]ethyl methanesulfonate 851627-61-7P 851627-63-9P, 2-[N-(2-Bromoethyl)-2-(6-tert-butoxy-8,8-dimethyl-6-oxido-5,7-dioxa-2-aza-6-phosphanonanoyl)-4,6-dinitroanilino]ethyl methanesulfonate 851627-65-1P, Di-tert-butyl
2-[[2-[bis(2-iodoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl phosphate 851627-67-3P 851627-69-5P,

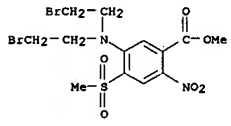
2-[N-(2-Chloroethyl)-3-(7-tert-butoxy-9,9-dimethyl-7-oxido-6,8-dioxa-2-aza-7-phosphahexanoyl)-2,4-dinitroanilino]ethyl methanesulfonate 851627-71-9P 851627-73-1P 851627-75-3P,

2-[N-(2-Bromoethyl)-3-(7-tert-butoxy-9,9-dimethyl-7-oxido-6,8-dioxa-2-aza-7-phosphahexanoyl)-2,4-dinitroanilino]ethyl methanesulfonate 851627-77-5P, 2-[N-(2-Iodoethyl)-3-(7-tert-butoxy-9,9-dimethyl-7-oxido-6,8-dioxa-2-aza-7-phosphahexanoyl)-2,4-dinitroanilino]ethyl methanesulfonate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)
RN 680199-25-1 CAPLUS
CN Benzamide, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

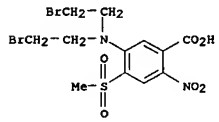


RN 680199-26-2 CAPLUS
CN Benzamide,
5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

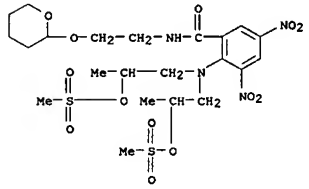
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-17-3 CAPLUS
CN Benzoic acid, 5-[bis(2-bromoethyl)amino]-4-(methylsulfonyl)-2-nitro- (9CI)
(CA INDEX NAME)

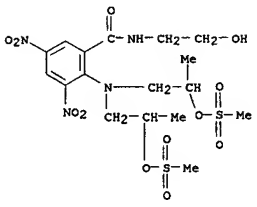


RN 851627-36-6 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]propyl]amino]-3,5-dinitro-N-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)

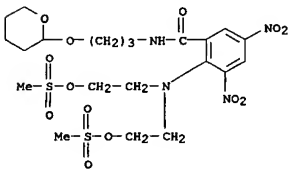


RN 851627-37-7 CAPLUS
CN Benzamide,
2-[bis[2-[(methylsulfonyl)oxy]propyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

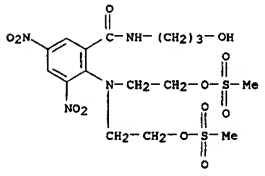
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



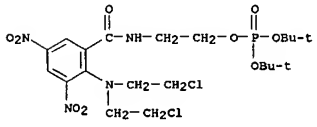
RN 851627-41-3 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[3-[(tetrahydro-2H-pyran-2-yl)oxy]propyl]- (9CI) (CA INDEX NAME)



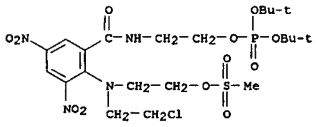
RN 851627-42-4 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



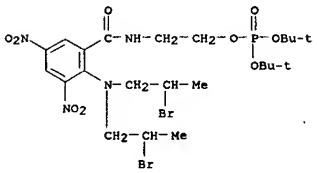
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-59-3 CAPLUS
CN Phosphoric acid, 2-[[2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



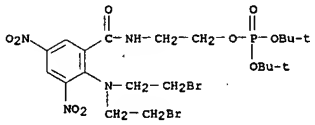
RN 851627-61-7 CAPLUS
CN Phosphoric acid, 2-[[2-[bis(2-bromopropyl)amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



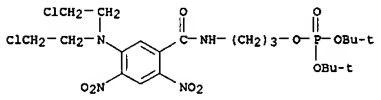
RN 851627-63-9 CAPLUS
CN Phosphoric acid, 2-[[2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

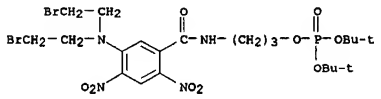
RN 851627-51-5 CAPLUS
CN Phosphoric acid, 2-[[2-[bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



RN 851627-53-7 CAPLUS
CN Phosphoric acid, 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]propyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

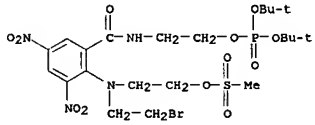


RN 851627-55-9 CAPLUS
CN Phosphoric acid, 3-[[5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzoyl]amino]propyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

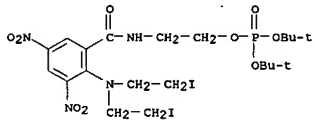


RN 851627-57-1 CAPLUS
CN Phosphoric acid, 2-[[2-[bis(2-chloroethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

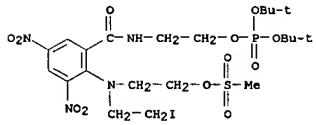
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-65-1 CAPLUS
CN Phosphoric acid, 2-[[2-[bis(2-iodoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

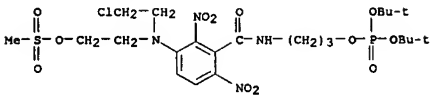


RN 851627-67-3 CAPLUS
CN Phosphoric acid, bis(1,1-dimethylethyl) 2-[[2-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]amino]ethyl ester (9CI) (CA INDEX NAME)

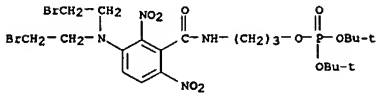


RN 851627-69-5 CAPLUS
CN Phosphoric acid, 3-[[3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitrobenzoyl]amino]propyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

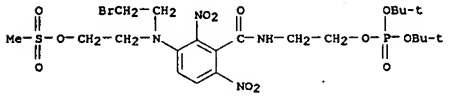
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-71-9 CAPLUS
CN Phosphoric acid, 3-[[3-[bis(2-bromoethyl)amino]-2,6-dinitrobenzoyl]amino]propyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

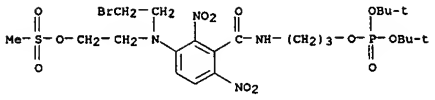


RN 851627-73-1 CAPLUS
CN Phosphoric acid, 2-[[3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitrobenzoyl]amino]ethyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

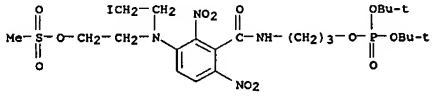


RN 851627-75-3 CAPLUS
CN Phosphoric acid, 3-[[3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitrobenzoyl]amino]propyl bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



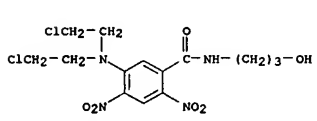
RN 851627-77-5 CAPLUS
CN Phosphoric acid, bis(1,1-dimethylethyl) 3-[[3-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitrobenzoyl]amino]propyl ester (9CI) (CA INDEX NAME)



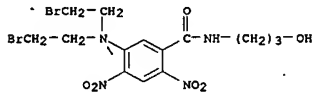
IT 444729-12-8P, N-(3-Hydroxypropyl)-5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzamide 444729-13-9P, N-(3-Hydroxypropyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide 680199-07-9P, 2-[N-(2-Iodoethyl)-2-[[(2-hydroxyethyl)amino]carbonyl]-4,6-dinitroanilino]ethyl methanesulfonate 680199-16-0P, 2-[N-(2-Chloroethyl)-3-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate 680199-57-9P, 2-[Bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide 851627-21-9P, 2-[Bis(2-Chloroethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide 851627-22-0P, 2-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide 851627-23-1P, 2-[Bis(2-chloroethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitrobenzamide 851627-26-4P, 2-[Bis(2-chloroethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitrobenzamide 851627-29-7P, 2-[Bis(2-chloroethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitrobenzamide 851627-32-2P, 2-[Bis(2-chloroethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitrobenzamide 851627-34-4P, 2-[Bis(2-bromopropyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide 851627-43-5P, 2-[N-(2-Chloroethyl)-2-[[(2-hydroxyethyl)amino]carbonyl]-4,6-dinitroanilino]ethyl methanesulfonate 851627-44-6P, 2-[N-(2-Bromoethyl)-3-[[(2-hydroxyethyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate 851627-45-7P, 3-[Bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-2,6-dinitrobenzamide 851627-46-8P, 2-[N-(2-Bromoethyl)-3-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate 851627-49-1P, 2-[N-(2-Iodoethyl)-3-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prodrug candidate; preparation of nitrophenyl mustard and aziridine alc.

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)

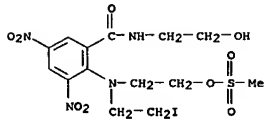
RN 444729-12-8 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(3-hydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



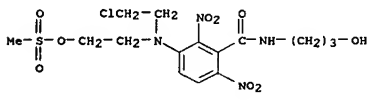
RN 444729-13-9 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 680199-07-9 CAPLUS
CN Benzamide, N-(2-hydroxyethyl)-2-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro- (9CI) (CA INDEX NAME)

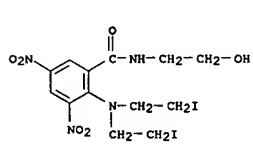


RN 680199-16-0 CAPLUS
CN Benzamide, 3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

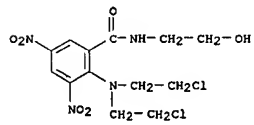


L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

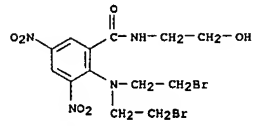
RN 680199-57-9 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI)
(CA INDEX NAME)



RN 851627-21-9 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

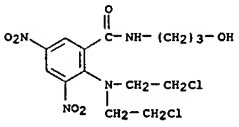


RN 851627-22-0 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

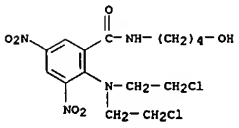


RN 851627-23-1 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

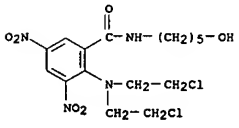
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-26-4 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

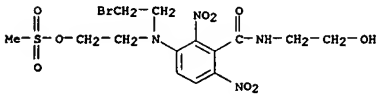


RN 851627-29-7 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

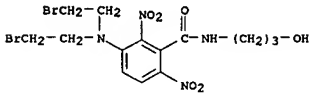


RN 851627-32-2 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

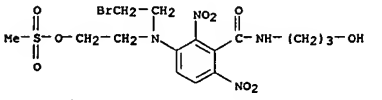
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



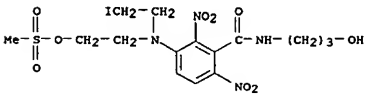
RN 851627-45-7 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)



RN 851627-46-8 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

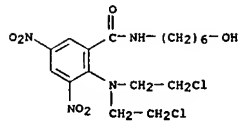


RN 851627-49-1 CAPLUS
CN Benzamide, N-(3-hydroxypropyl)-3-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

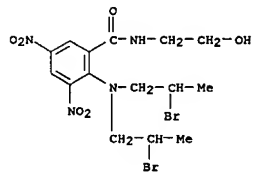


IT 680199-02-4P, 2-[N-(2-Bromoethyl)-5-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate 680199-06-8P, 2-[N-(2-Bromoethyl)-2-[[(2-hydroxyethyl)amino]carbonyl]-4,6-dinitroanilino]ethyl methanesulfonate 680199-41-1P, 3-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,6-dinitrobenzamide 680199-52-4P, N-(2-Hydroxyethyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide 851627-10-6P,

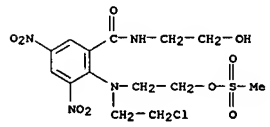
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-34-4 CAPLUS
CN Benzamide, 2-[bis(2-bromopropyl)amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 851627-43-5 CAPLUS
CN Benzamide, 2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

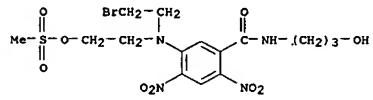


RN 851627-44-6 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

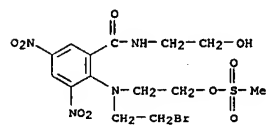
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

N-(4-Hydroxybutyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide 851627-11-7P, N-(5-Hydroxypentyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide 851627-12-8P, N-(6-Hydroxyhexyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide 851627-13-9P, 5-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-4-(methylsulfonyl)-2-nitrobenzamide 851627-18-4P, 5-[Bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-2,4-dinitrobenzamide 851627-24-2P, 2-[Bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitrobenzamide 851627-27-5P, 2-[Bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitrobenzamide 851627-30-0P, 2-[Bis(2-bromoethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitrobenzamide 851627-33-3P, 2-[Bis(2-bromoethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitrobenzamide 851627-38-8P, 2-[N-(2-Bromoethyl)-2-[[(3-hydroxypropyl)amino]carbonyl]-4,6-dinitroanilino]ethyl methanesulfonate 851627-47-9P, 3-[Bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-2,6-dinitrobenzamide 851627-48-0P, 2-[N-(2-Bromoethyl)-3-[[(4-hydroxybutyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodrug candidate; prepn. of nitrophenyl mustard and aziridine alc. prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)

RN 680199-02-4 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

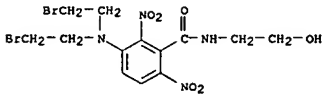


RN 680199-06-8 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

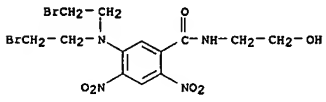


RN 680199-41-1 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-52-4 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 851627-10-6 CAPLUS
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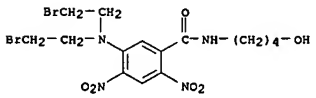
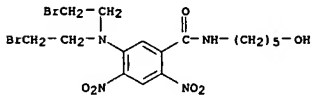
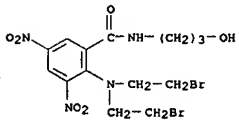


RN 851627-11-7 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-N-(5-hydroxypentyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

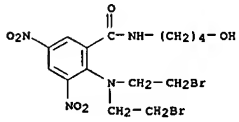


RN 851627-12-8 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-N-(6-hydroxyhexyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

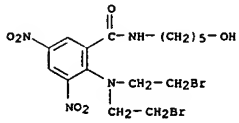
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



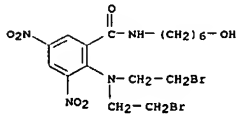
RN 851627-27-5 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



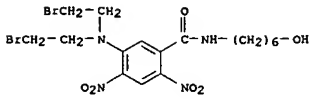
RN 851627-30-0 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 851627-33-3 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 851627-13-9 CAPLUS
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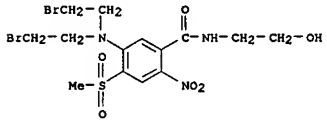

RN 851627-18-4 CAPLUS
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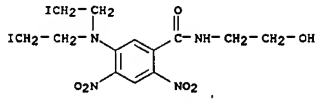
(CA INDEX NAME)



RN 851627-24-2 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 851627-38-8 CAPLUS
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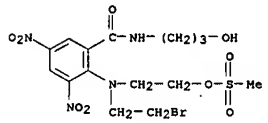
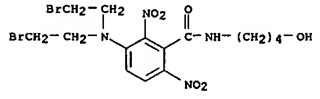
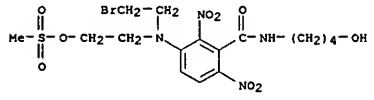


RN 851627-47-9 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

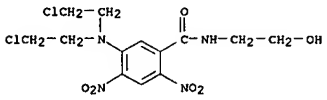


RN 851627-48-0 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(4-hydroxybutyl)-2,6-dinitro- (9CI) (CA INDEX NAME)



IT 150271-99-1, N-(2-Hydroxyethyl)-5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug candidate; preparation of nitrophenyl mustard and aziridine alc.
prodrugs and their corresponding phosphate pre-prodrugs and their use as targeted cytotoxic agents)
RN 150271-99-1 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

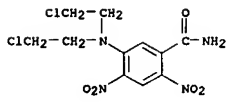
L9 ANSWER 4 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 5 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L9 ANSWER 5 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:614954 CAPLUS
DOCUMENT NUMBER: 145:89711
TITLE: Manufacture of conjugate of target protein and biological reductant used for antitumor treatment
INVENTOR(S): Hu, Yiqiao; Wu, Jinhui; Luo, Lingying; Zhi, Feng
PATENT ASSIGNEE(S): Nanjing University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1686562	A	20051026	CN 2005-10038631	20050331
WO 2006102854	A1	20061005	WO 2006-CN582	20060331

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: CN 2005-10038631 A 20050331

AB The title conjugate is manufactured from a target protein with effectivity on antitumor treatment and a biol. reductant, wherein the target protein is selected from transferrin, somatostatin, epidermal growth factor, folic acid, and transcobalamin, and the biol. reductant is selected from bifunctional nitro-heterocyclic compds., quinone compds., heterocyclic oxynitride, topoisomerase II inhibitor, and DNA targeted medicines. The conjugate is manufactured by: (1) adding the biol. reductant dropwise into a conjugating agent to obtain a mixture, and (2) adding the mixture to the target protein to obtain the conjugate. The conjugate can be used for manufacturing antitumor medicines.

IT 142439-61-0, SN23862
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(manufacture of conjugate of target protein and biol. reductant used for antitumor treatment)

RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

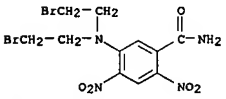
L9 ANSWER 6 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:465003 CAPLUS
DOCUMENT NUMBER: 143:159026
TITLE: Nitroarylmethylcarbamate prodrugs of doxorubicin for use with nitroreductase gene-directed enzyme prodrug therapy
AUTHOR(S): Hay, Michael P.; Wilson, William R.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, 92019, N. Z.
SOURCE: Bioorganic & Medicinal Chemistry (2005), 13(12), 4043-4055
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:159026

AB A series of nitrobenzyl- and nitroimidazolylmethyl carbamate prodrugs of doxorubicin were prepared and evaluated for their potential use in nitroreductase (NTR) mediated gene-directed enzyme prodrug therapy (GDEPT). The carbamate prodrugs and doxorubicin were tested in a cell line panel comprising parental and NTR transfected human (SKOV3/SKOV3-NTRneo, WiDr/WiDr-NTRneo), Chinese hamster (V79/V79-NTRpuro) and murine (EMT6/EMT6-NTRpuro) cell line pairs, and were compared with the established NTR substrates CB 1954 (an aziridinyl dinitrobenzamide) and the analogous dibromomustard SN 29427. The low solubility of the prodrugs (from 3 to 39 μM) precluded the determination of IC50 values against the parent cell lines in some instances. All of the prodrugs were unstable in culture medium with 5% added fetal calf serum over a 24 h period, although release of doxorubicin was not observed The prodrugs were 20- to > 336-fold less toxic than doxorubicin in the human cells lines SKOV3 and WiDr, with overall less deactivation seen in the V79 cell line (11- to > 286-fold) and EMT6 cell line (1.8- to > 178-fold). Prodrugs with the nitrobenzyl unit directly conjugated to doxorubicin showed modest selectivity for NTR across the cell line panel (1- to 5.9-fold) but this was increased to between > 10- and > 370-fold with the interpolation of an 4-aminobenzyl spacer unit between the bioreductive unit and doxorubicin. A 2-nitroimidazolylmethyl carbamate provided deactivation of doxorubicin (8- to 124-fold) but showed only modest selectivity for NTR (2- to 14-fold) across the panel. The interpolation of a 4-aminobenzyl spacer gave slightly lower deactivation (3- to 64-fold) and similar selectivity for NTR (> 1.2- to > 12-fold) for 2- and 5-nitroimidazolylmethyl prodrugs. The activity of two nitrobenzyl prodrugs containing an aminobenzyl spacer, providing excellent selectivity for NTR+ve cells in culture, was evaluated against EMT6 tumors comprising ca. 10% NTR+ve cells, but neither showed statistically significant levels of killing even of NTR+ve cells. This lack of activity in tumors, despite potent and selective activity in culture, indicates that pharmacokinetic optimization is needed to achieve in vivo efficacy against solid tumors with this new class of NTR prodrugs.

IT 150271-87-7

L9 ANSWER 6 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroarylmethylcarbamate prodrugs of doxorubicin for use with nitroreductase gene-directed enzyme prodrug therapy)
RN 150271-87-7 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



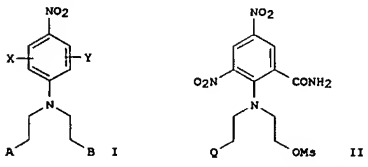
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:333688 CAPLUS
DOCUMENT NUMBER: 140:339059
TITLE: Preparation of nitroaniline-based unsymmetrical mustard alkylating agents as prodrugs
INVENTOR(S): Denny, William Alexander; Atwell, Graham J.; Yang, Shangjin; Wilson, William Robert
PATENT ASSIGNEE(S): Auckland Uniservices Limited, N. Z.
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033415	A1	20040422	WO 2003-NZ225	20031008
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NZ 521851	A	20050225	NZ 2002-521851	20021008
CA 2501388	A1	20040422	CA 2003-2501388	20031008
AU 2003278628	A1	20040504	AU 2003-278628	20031008
EP 1558568	A1	20050803	EP 2003-770163	20031008
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1711236	A	20051221	CN 2003-80102812	20031008
JP 2006502214	T	20060119	JP 2004-542927	20031008
IN 2005KN00776	A	20060707	IN 2005-KN776	20050502
US 2005256191	A1	20051117	US 2005-529772	20050602
PRIORITY APPLN. INFO.:			NZ 2002-521851 A	20021008
			WO 2003-NZ225 W	20031008

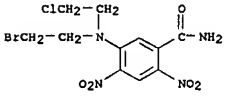
OTHER SOURCE(S): MARPAT 140:339059
GI

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

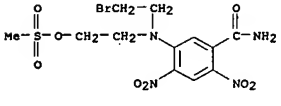


AB Title compds. [I; X = NO2, cyano, SO2R1; R1 = alkyl, hydroxyalkyl, aminoalkyl; Y = OR2, NHCOR2, CONR2CO2R3, CONHR2, SO2NH2, SO2NHR2, etc.; R2, R3 = H, alkyl, hydroxyalkyl, aminoalkyl; A, B = halo, OSO2R4, OSO2NH2, OSO2NHR4, etc.; R4 = alkyl, hydroxyalkyl, aminoalkyl; A ≠ B; with one specific exclusion], were prepared for use as prodrugs for gene-dependent enzyme prodrug therapy (GDEPT) and cell ablation therapy in conjunction with nitroreductase enzymes as hypoxia selective cytotoxins and as anticancer agents. Thus, aniline (II; Q = MsO) (preparation given) was stirred with LiBr in EtOAc at 60° for 2 h to give 53% II (Q = Br) (III) and 20% dibromide. III showed an IC50 = 6.0 μM against human SKOV3 ovarian cancer cells.
IT 680198-98-5P, 5-[(2-Bromoethyl)(2-chloroethyl)amino]-2,4-dinitrobenzamide 680198-99-6P, 2-[5-(Aminocarbonyl)-N-(2-bromoethyl)-2,4-dinitroanilino]ethyl methanesulfonate 680199-00-2P, 2-[5-(Aminocarbonyl)-N-(2-iodoethyl)-2,4-dinitroanilino]ethyl methanesulfonate 680199-01-3P, 2-(N-(2-Bromoethyl)-5-[[(2-hydroxyethyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-02-4P, 2-(N-(2-Bromoethyl)-5-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-03-5P, 2-(N-(2-Bromoethyl)-5-[[(2,3-dihydroxypropyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-04-6P, 2-[2-(Aminocarbonyl)-N-(2-chloroethyl)-4,6-dinitroanilino]ethyl methanesulfonate 680199-05-7P, 2-[2-(Aminocarbonyl)-N-(2-bromoethyl)-4,6-dinitroanilino]ethyl methanesulfonate 680199-06-8P, 2-(N-(2-Bromoethyl)-2-[[(2-hydroxyethyl)amino]carbonyl]-4,6-dinitroanilino)ethyl methanesulfonate 680199-07-9P, 2-(N-(2-Iodoethyl)-2-[[(2-hydroxyethyl)amino]carbonyl]-4,6-dinitroanilino)ethyl methanesulfonate 680199-08-0P, 2-(N-(2-Bromoethyl)-2-[[(2-hydroxypropyl)amino]carbonyl]-4,6-dinitroanilino)ethyl methanesulfonate 680199-09-1P, 2-(N-(2-Bromoethyl)-2-[[(2,3-dihydroxypropyl)amino]carbonyl]-4,6-dinitroanilino)ethyl methanesulfonate 680199-10-4P, 2-(N-(2-Bromoethyl)-2-[[(3-(4-morpholinyl)propyl)amino]carbonyl]-4,6-dinitroanilino)ethyl methanesulfonate 680199-11-5P, Methyl 3-[[2-((2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino)-3,5-dinitrobenzoyl]amino]propanoate 680199-12-6P, Methyl 3-[[2-((2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino)-3,5-dinitrobenzoyl]amino]propanoate 680199-13-7P, 2-[3-(Aminocarbonyl)-N-(2-chloroethyl)-2,4-dinitroanilino]ethyl methanesulfonate 680199-16-0P, 2-(N-(2-Chloroethyl)-3-[[(3-hydroxypropyl)amino]carbonyl]-2,4-

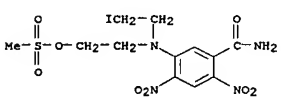
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
dinitroanilino)ethyl methanesulfonate 680199-19-3P, 2-(N-(2-Chloroethyl)-3-[[(2,3-dihydroxypropyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-20-6P, 2-(N-(2-Bromoethyl)-3-[[(2,3-dihydroxypropyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-21-7P, 2-(N-(2-Chloroethyl)-3-[[(3-(4-morpholinyl)propyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate 680199-22-8P, 2-(N-(2-Bromoethyl)-3-[[(3-(4-morpholinyl)propyl)amino]carbonyl]-2,4-dinitroanilino)ethyl methanesulfonate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of nitroaniline-based unsym. mustard alkylating agents as prodrugs)
RN 680198-98-5 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 680198-99-6 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

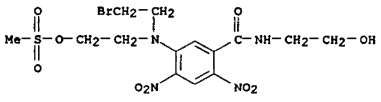


RN 680199-00-2 CAPLUS
CN Benzamide, 5-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

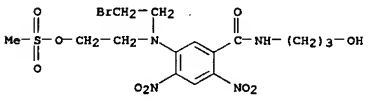


RN 680199-01-3 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-

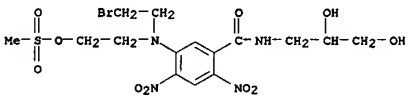
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



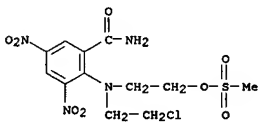
RN 680199-02-4 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



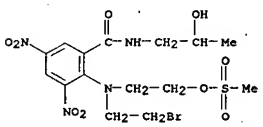
RN 680199-03-5 CAPLUS
CN Benzamide, 5-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



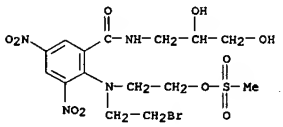
RN 680199-04-6 CAPLUS
CN Benzamide, 2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



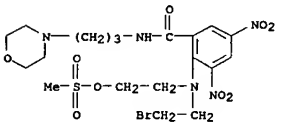
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



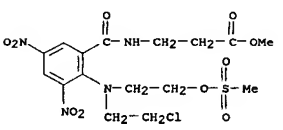
RN 680199-09-1 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 680199-10-4 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[3-(4-morpholinyl)propyl]-3,5-dinitro- (9CI) (CA INDEX NAME)

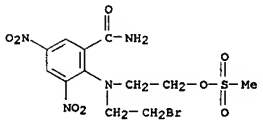


RN 680199-11-5 CAPLUS
CN β-Alanine, N-[2-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)

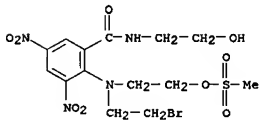


L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

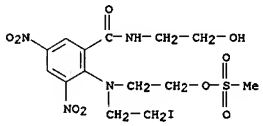
RN 680199-05-7 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 680199-06-8 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



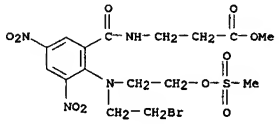
RN 680199-07-9 CAPLUS
CN Benzamide, N-(2-hydroxyethyl)-2-[(2-iodoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



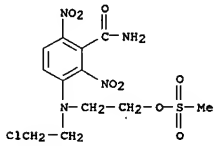
RN 680199-08-0 CAPLUS
CN Benzamide, 2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

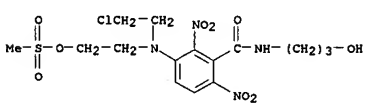
RN 680199-12-6 CAPLUS
CN β-Alanine, N-[2-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 680199-13-7 CAPLUS
CN Benzamide, 3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

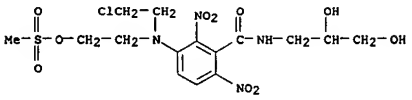


RN 680199-16-0 CAPLUS
CN Benzamide, 3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

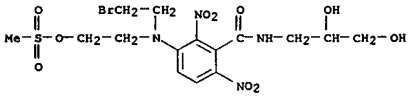


RN 680199-19-3 CAPLUS
CN Benzamide, 3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)

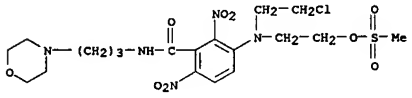
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



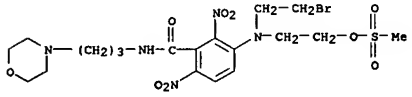
RN 680199-20-6 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)



RN 680199-21-7 CAPLUS
CN Benzamide,
3-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[3-(4-morpholinyl]propyl]-2,6-dinitro- (9CI) (CA INDEX NAME)

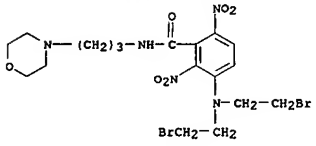


RN 680199-22-8 CAPLUS
CN Benzamide, 3-[(2-bromoethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[3-(4-morpholinyl)propyl]-2,6-dinitro- (9CI) (CA INDEX NAME)

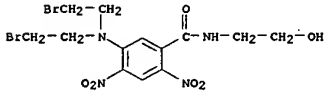


IT 188719-23-5P 444729-14-0P 680199-41-1P,
3-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,6-dinitrobenzamide

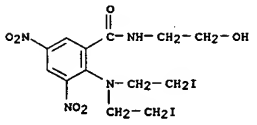
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



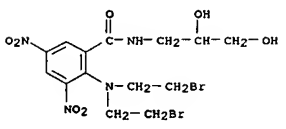
RN 680199-52-4 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



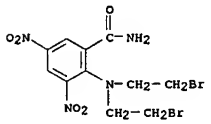
RN 680199-57-9 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI)
(CA INDEX NAME)



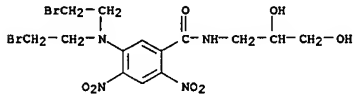
RN 680199-59-1 CAPLUS
CN Benzamide,
2-[bis(2-bromoethyl)amino]-N-(2,3-dihydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)



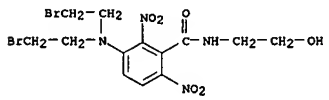
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
680199-50-2P 680199-52-4P 680199-57-9P
680199-59-1P 680199-61-5P 680199-65-9P
680199-67-1P 680199-69-3P 680199-77-3P
RL: BYP (Byproduct); PREP (Preparation)
(prepn. of nitroaniline-based unsym. mustard alkylating agents as prodrugs)
RN 188719-23-5 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 444729-14-0 CAPLUS
CN Benzamide,
5-[bis(2-bromoethyl)amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



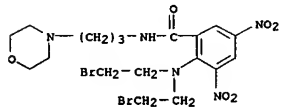
RN 680199-41-1 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,6-dinitro- (9CI) (CA INDEX NAME)



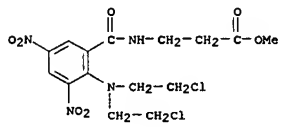
RN 680199-50-2 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-N-[3-(4-morpholinyl)propyl]-2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

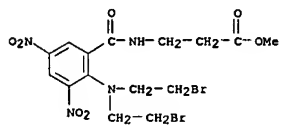
RN 680199-61-5 CAPLUS
CN Benzamide, 2-[bis(2-bromoethyl)amino]-N-[3-(4-morpholinyl)propyl]-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 680199-65-9 CAPLUS
CN β-Alanine, N-[2-[bis(2-chloroethyl)amino]-3,5-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)

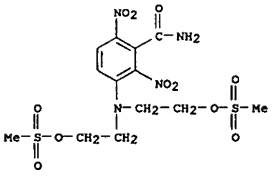


RN 680199-67-1 CAPLUS
CN β-Alanine, N-[2-[bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)

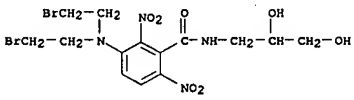


RN 680199-69-3 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

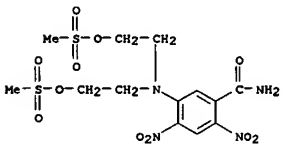
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



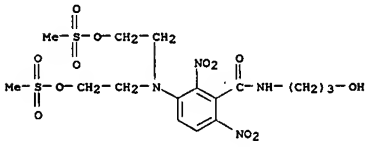
RN 680199-77-3 CAPLUS
CN Benzamide,
3-[bis(2-bromoethyl)amino]-N-(2,3-dihydroxypropyl)-2,6-dinitro-
(9CI) (CA INDEX NAME)



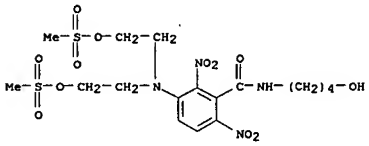
IT 150271-89-9, 2-[5-(Aminocarbonyl)-N-[2-[(methylsulfonyl)oxy]ethyl]-
2,4-dinitroanilino]ethyl methanesulfonate 169527-43-9,
2-[5-(Aminocarbonyl)-N-(2-chloroethyl)-2,4-dinitroanilino]ethyl
methanesulfonate 680199-42-2 680199-44-4
680199-46-6 680199-47-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitroaniline-based unsym. mustard alkylating agents as
prodrugs)
RN 150271-89-9 CAPLUS
CN Benzamide, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro- (9CI)
(CA INDEX NAME)



L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

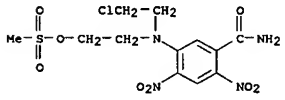


RN 680199-47-7 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(4-hydroxybutyl)-
2,6-dinitro- (9CI) (CA INDEX NAME)

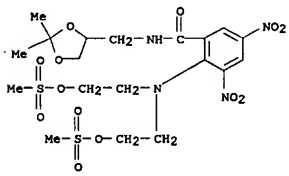


IT 680199-23-9P, Methyl 5-(bis[2-[(methylsulfonyl)oxy]ethyl]amino)-
2,4-dinitrobenzoate 680199-24-0P, 5-(Bis[2-
[(methylsulfonyl)oxy]ethyl]amino)-2,4-dinitrobenzoic acid
680199-25-1P, 2-(5-[[(2-Hydroxyethyl)amino]carbonyl]-N-[2-
[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino)ethyl methanesulfonate
680199-26-2P, 2-(5-[[(3-Hydroxypropyl)amino]carbonyl]-N-[2-
[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino)ethyl methanesulfonate
680199-27-3P, 2-(5-[[(2,3-Dihydroxypropyl)amino]carbonyl]-N-[2-
[(methylsulfonyl)oxy]ethyl]-2,4-dinitroanilino)ethyl methanesulfonate
680199-28-4P, 2-(2-(Aminocarbonyl)-N-(2-
[(methylsulfonyl)oxy]ethyl]-4,6-dinitroanilino)ethyl methanesulfonate
680199-31-9P 680199-34-2P 680199-35-3P
680199-36-4P 680199-37-5P 680199-39-7P, Methyl
3-(bis[2-[(methylsulfonyl)oxy]ethyl]amino)-2,6-dinitrobenzoate
680199-40-0P, 3-[Bis(2-bromoethyl)amino]-2,6-dinitrobenzamide
680199-45-5P, 3-(Bis[2-[(methylsulfonyl)oxy]ethyl]amino)-2,6-
dinitrobenzoic acid 680199-48-8P 680199-55-7P
680199-63-7P 680199-75-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of nitroaniline-based unsym. mustard alkylating agents as
prodrugs)
RN 680199-23-9 CAPLUS
CN Benzoic acid, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro-,
methyl ester (9CI) (CA INDEX NAME)

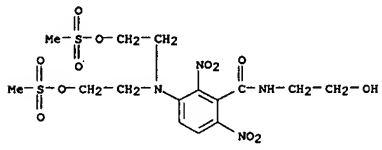
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 169527-43-9 CAPLUS
CN Benzamide, 5-[(2-chloroethyl)[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-
dinitro- (9CI) (CA INDEX NAME)



RN 680199-42-2 CAPLUS
CN Benzamide,
2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[(2,2-dimethyl-1,3-
dioxolan-4-yl)methyl]-3,5-dinitro- (9CI) (CA INDEX NAME)

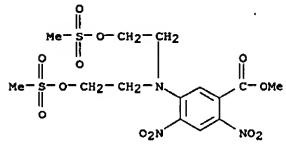


RN 680199-44-4 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-
2,6-dinitro- (9CI) (CA INDEX NAME)

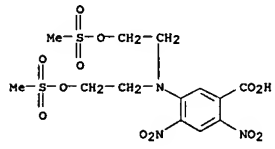


RN 680199-46-6 CAPLUS
CN Benzamide,
3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-
2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-24-0 CAPLUS
CN Benzoic acid, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro-
(9CI) (CA INDEX NAME)



RN 680199-25-1 CAPLUS
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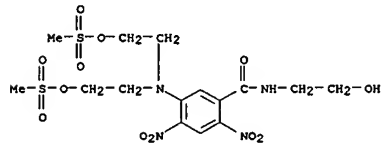
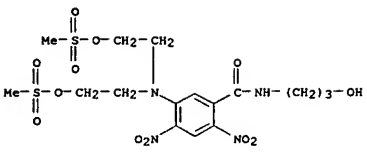
2,4-dinitro- (9CI) (CA INDEX NAME)

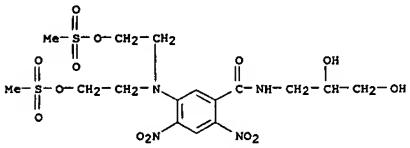


RN 680199-26-2 CAPLUS
CN Benzamide,
5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(3-hydroxypropyl)-
2,4-dinitro- (9CI) (CA INDEX NAME)

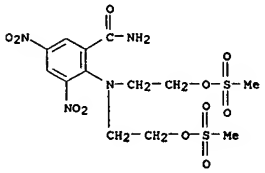
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-27-3 CAPLUS
CN Benzamide, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

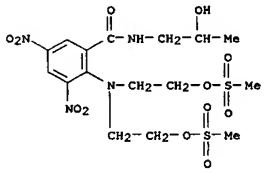


RN 680199-28-4 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro- (9CI) (CA INDEX NAME)

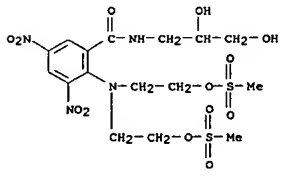


RN 680199-31-9 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxyethyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

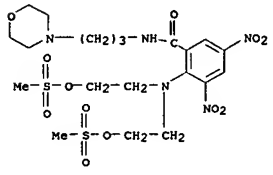
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-36-4 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-dihydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

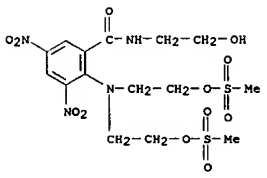


RN 680199-37-5 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[3-(4-morpholinyl)propyl]-3,5-dinitro- (9CI) (CA INDEX NAME)

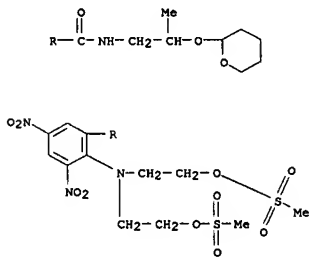


RN 680199-39-7 CAPLUS
CN Benzoic acid, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro-, methyl ester (9CI) (CA INDEX NAME)

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

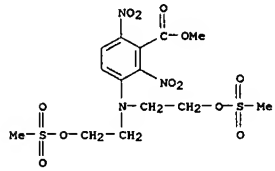


RN 680199-34-2 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-[(tetrahydro-2H-pyran-2-yl)oxy]propyl]- (9CI) (CA INDEX NAME)

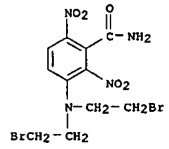


RN 680199-35-3 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2-hydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

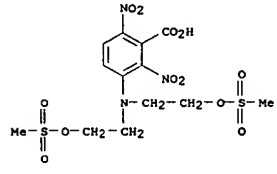
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-40-0 CAPLUS
CN Benzamide, 3-[bis(2-bromoethyl)amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

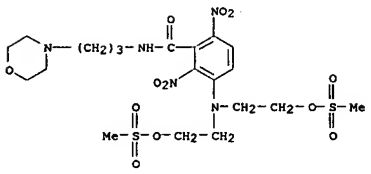


RN 680199-45-5 CAPLUS
CN Benzoic acid, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

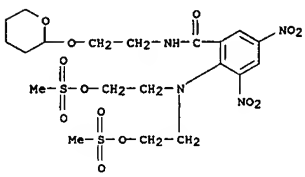


RN 680199-48-8 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-[3-(4-morpholinyl)propyl]-2,6-dinitro- (9CI) (CA INDEX NAME)

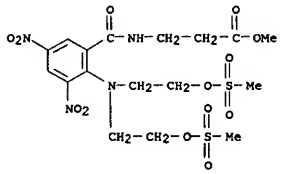
L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 680199-55-7 CAPLUS
CN Benzamide, 2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitro-N-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]- (9CI) (CA INDEX NAME)

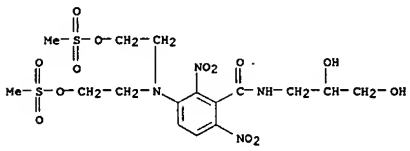


RN 680199-63-7 CAPLUS
CN β-Alanine, N-[2-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-3,5-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 680199-75-1 CAPLUS
CN Benzamide, 3-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-N-(2,3-

L9 ANSWER 7 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
dihydroxypropyl)-2,6-dinitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L9 ANSWER 8 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:60025 CAPLUS
DOCUMENT NUMBER: 140:124550
TITLE: Cloning, sequences and characterization of microbial nitroreductases and their use for converting CB1954 into anticancer drugs
INVENTOR(S): Minton, Nigel; Anlezark, Gill; Vaughan, Thomas
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 36 pp., Cont.-in-part of U.S. Ser. No. 913,068, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004014191	A1	20040122	US 2003-364397	20030212
WO 2000047725	A1	20000817	WO 2000-GB431	20000210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

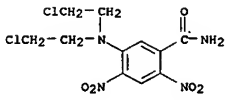
PRIORITY APPLN. INFO.:		
GB 1999-3019	A	19990210
WO 2000-GB431	W	20000210
US 2001-913068	B2	20011228

AB The nucleotide sequences and the encoded amino acid sequences of a number of microbial nitroreductases are provided. Phys. characteristics and kinetic properties of the nitroreductases are reported. The nitroreductases of the invention demonstrate preferential catalytic conversion of the alkylating agent CB1954 into its highly cytotoxic 4-hydroxylamine (4HX) derivative, this derivative demonstrating anticarcinoma properties. Accordingly, the catalytic activity of the nitroreductase enzymes of the present invention may be employed to achieve catalysis of CB1954 into its cytotoxic derivative in a site-directed manner, such as by Directed-Enzyme Prodrug Therapy (DEPT).

IT 142439-61-0, SN23862
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cloning, sequences and characterization of microbial nitroreductases and their use for converting CB1954 into anticancer drugs)

RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

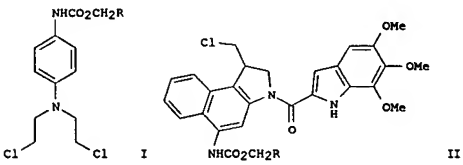
L9 ANSWER 8 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L9 ANSWER 9 OF 47 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004105275 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14997211
TITLE: 2-Amino metabolites are key mediators of CB 1954 and SN 23862 bystander effects in nitroreductase GDEPT.
AUTHOR: Helsby N A; Ferry D M; Patterson A V; Pullen S M; Wilson W R
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand.
SOURCE: British journal of cancer, (2004 Mar 8) Vol. 90, No. 5, pp. 1084-92.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 4 Mar 2004
Last Updated on STN: 30 Apr 2004
Entered Medline: 29 Apr 2004

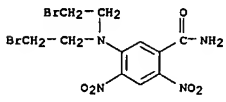
AB An important feature of gene-directed enzyme-prodrug therapy is that prodrug activation can provide diffusible cytotoxic metabolites capable of generating a local bystander effect in tumours. Activation of the aziridinyl dinitrobenzamide CB 1954 by E. coli nitroreductase (NTR) provides a bystander effect assumed to be due to the potently cytotoxic 4-hydroxylamine metabolite. We show that there are four cytotoxic extracellular metabolites of CB 1954 in cultures of NTR-expressing tumour cells (the 2- and 4-hydroxylamines and their corresponding amines). The 4-hydroxylamine is the most cytotoxic in DNA crosslink repair defective cells, but the 2-amino derivative (CB 10-236) is of similar potency to the 4-hydroxylamine in human tumour cell lines. Importantly, CB 10-236 has much superior diffusion properties to the 4-hydroxylamine in multicellular layers grown from the SiHa human cervical carcinoma cell line. These results suggest that the 2-amine, not the 4-hydroxylamine, is the major bystander metabolite when CB 1954 is activated by NTR in tumours. The corresponding dinitrobenzamide nitrogen mustard SN 23862 is reduced by NTR to form a single extracellular metabolite (also the 2-amine), which has superior cytotoxic potency and diffusion properties to the CB 1954 metabolites. These results are consistent with the reported high bystander efficiency of SN 23862 as an NTR prodrug in multicellular layers and tumour xenografts.

L9 ANSWER 10 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:851484 CAPLUS
DOCUMENT NUMBER: 140:59485
TITLE: Synthesis and Evaluation of Nitroheterocyclic Carbamate Prodrugs for Use with Nitroreductase-Mediated Gene-Directed Enzyme Prodrug Therapy
AUTHOR(S): Hay, Michael P.; Anderson, Robert F.; Ferry, Dianne M.; Wilson, William R.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2003), 46(25), 5533-5545
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:59485
GI



AB A variety of nitroheteroaryl-substituted carbamate prodrugs of phenylenediamine mustard I (R = 5-nitro-2-furyl, 5-nitro-2-thienyl, 1-methyl-2-nitroimidazol-5-yl, 1-methyl-5-nitroimidazol-2-yl) and 5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3H-benz[e]indoline (amino-seco-CBI-TMI) II, covering a wide range of reduction potential, were prepared and evaluated for use in gene-directed enzyme prodrug therapy (GDEPT) using a two-electron nitroreductase (NTR) from Escherichia coli B. These carbamate prodrugs and the corresponding amine effectors were tested in a cell line panel comprising parental and NTR-transfected human (SKOV3/SKOV3-NTRneo, WiDr/WiDr-NTRneo), Chinese hamster (V79puro/V79-NTRpuro), and murine (EMT6/EMT6-NTRpuro) cell line pairs and were compared with the established NTR substrates CB1954 (5-(1-aziridinyl)-2,4-dinitrobenzamide) and the analogous dibromo mustard. I (R = 1-methyl-2-nitroimidazol-5-yl) was metabolized rapidly by EMT6-NTRneo but not EMT6 cells, demonstrating that it is an efficient substrate for NTR. Despite this, the carbamates of phenylenediamine mustards I show relatively low differential cytotoxicity for NTR+ve cells in IC50 assays, apparently because they retain sufficient alkylating reactivity that most of the prodrug reacts with nucleophiles during the

L9 ANSWER 10 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
drug exposure period. In contrast, the corresponding prodrugs II were less efficient NTR substrates but had greater chem. stability, were more potent, and showed substantial NTR-ve/NTR+ve ratios in the cell line panel, with ratios of 15-100-fold for the II (R = 1-methyl-2-nitroimidazol-5-yl) and II (R = 1-methyl-5-nitroimidazol-2-yl). The activity of these two prodrugs was evaluated against NTR-expressing EMT6 tumors comprising ca. 10% NTR+ve cells. Small but not statistically significant killing of NTR+ve cells was obsd., with no effect against NTR-ve target cells. The lack of activity against NTR+ve cells in tumors, despite potent and selective activity in culture, indicates that pharmacokinetic optimization will be required if in vivo efficacy against solid tumors is to be achieved with this new class of NTR prodrugs.
IT 150271-87-7
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation and biol. evaluation of nitroheteroaryl-substituted carbamates of phenylenediamine mustards and amino(chloromethyl)dihydro(indolylcarbonyl)benz[e]indoles for use with nitroreductase-mediated gene-directed enzyme prodrug therapy)
RN 150271-87-7 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 47 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003482056 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12954054
TITLE: Studies on the nitroreductase prodrug-activating system. Crystal structures of complexes with the inhibitor dicoumarol and dinitrobenzamide prodrugs and of the enzyme active form.
AUTHOR: Johansson Eric; Parkinson Gary N; Denny William A; Neidle Stephen
CORPORATE SOURCE: Cancer Research UK Biomolecular Structure Group, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom.
SOURCE: Journal of medicinal chemistry, (2003 Sep 11) Vol. 46, No. 19, pp. 4009-20.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 17 Oct 2003
Last Updated on STN: 11 Nov 2003
Entered Medline: 10 Nov 2003

AB The E. coli nitroreductase enzyme (NTR) has been widely used in suicide gene therapy (GDEPT and ADEPT) applications as a activating enzyme for nitroaromatic prodrugs of the dinitrobenzamide class. NTR has been previously shown to be a homodimeric enzyme with two active sites. We present here the crystal structures of the reduced form of NTR and its complexes with the inhibitor dicoumarol and three dinitrobenzamide prodrugs. Comparison of the structures of the oxidized and reduced forms of the native enzyme shows that the principal structural changes occur in the FMN cofactor and indicate that the enzyme itself is a relatively rigid structure that primarily provides a rigid structural framework on which hydride transfer occurs. The aziridinyldinitrobenzamide prodrug CB 1954 binds in nonidentical ways in both of the two active sites of the homodimeric enzyme, employing both hydrophobic and (in active site B) a direct H-bond contact to the side chain of Lys14. In active site A the 2-nitro group stacks above the FMN, and in active site B the 4-nitro group does, explaining why reduction of either nitro group is observed. In contrast, the larger mustard group of the dinitrobenzamide mustard compound SN 23862 forces the prodrug to bind at both active sites with only the 2-nitro group able to participate in hydride transfer from the FMN, explaining why only the 2-hydroxylamine reduction product is observed. In each site, the nitro groups of the prodrug make direct H-bond contacts with the enzyme; in active Site A the 2-nitro to Ser40 and the 4-nitro to Asn71, while in active Site B the 2-nitro contacts the main chain nitrogen of Thr41 and the 4-nitro group the Lys14 side chain. The related amide-substituted mustard SN 27217 binds in a broadly similar fashion, but with the larger amide group substituent able to reach and contact the side chain of Arg107, further restricting the prodrug conformations in the binding site. The inhibitor dicoumarol appears to bind primarily by pi-stacking interactions and hydrophobic contacts, with no conformational changes in the enzyme. One of the hydroxycoumarin

L9 ANSWER 11 OF 47 MEDLINE on STN DUPLICATE 2
(Continued)
subunits stacks above the plane of the FMN via pi-overlap with the isoalloxazine ring, penetrating deep into the groove, with the other less well-defined. These studies suggest guidelines for further prodrug design. Steric bulk (e.g., mustard rather than aziridine) on the ring can limit the possible binding orientations, and the reducible nitro group must be located para to the mustard. Substitution on the carboxamide side chain still allows the prodrugs to bind, but also limits their orientation in the binding site. Finally, modulating substrate specificity by alteration of the structure of the enzyme rather than the prodrug might usefully focus on modifying the Phe124 residue and those surrounding it.

L9 ANSWER 12 OF 47 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003185362 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12703963
TITLE: Effect of nitroreduction on the alkylating reactivity and cytotoxicity of the 2,4-dinitrobenzamide-5-aziridine CB 1954 and the corresponding nitrogen mustard SN 23862: distinct mechanisms of bioreductive activation.
AUTHOR: Helsby Nuala A; Wheeler S James; Pruijn Frederik B; Palmer Brian D; Yang Shangjin; Denny William A; Wilson William R
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, Private Bag 92019, Auckland, New Zealand.. n.helsby@auckland.ac.nz
SOURCE: Chemical research in toxicology, (2003 Apr) Vol. 16, No. 4, pp. 469-78.
Journal code: 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 22 Apr 2003
Last Updated on STN: 24 Mar 2004
Entered Medline: 23 Mar 2004

AB The dinitrobenzamide aziridine CB 1954 (1) and its nitrogen mustard analogue SN 23862 (6) are prodrugs that are activated by enzymatic nitroreduction in tumors. Bioactivation of 1 is considered to be due to reduction of its 4-nitro group to the hydroxylamine and subsequent formation of the N-acetoxy derivative; this acts as a reactive center, in concert with the aziridine moiety, to provide a bifunctional DNA cross-linking agent (Knox model). It is currently unclear whether bioactivation of 6 occurs by the same mechanism or results from the electronic effects of nitroreduction on reactivity of the nitrogen mustard moiety. To discriminate between these mechanisms, we have synthesized the hydroxylamine and amine derivatives of 1 and 6, plus related compounds, and determined their alkylating reactivities in aqueous solution, using LC/MS to identify reaction pathways. The relationships between substituent electronic effects, reactivity, and cytotoxicity were determined using the UV4 cell line, which is defective in nucleotide excision repair (thus avoiding differences in repair kinetics). Alkylating reactivity correlated with the electron-donating character of the ortho or para substituent in the case of the mustards, with a less marked electronic effect for the aziridines. Importantly, there was a highly significant linear relationship between cytotoxic potency and alkylating reactivity in both the aziridine and the mustard series, with the notable exception of 4, the 4-hydroxylamine of 1, which was 300-fold more toxic than predicted by this relationship. This demonstrates that the high potency of 4 does not result from activation of the aziridine ring, supporting the Knox model. The single-step bioactivation of 6, to amino or hydroxylamine metabolites with similar potency to 4, is a potential advantage in the use of dinitrobenzamide mustards as prodrugs for activation by nitroreductases.

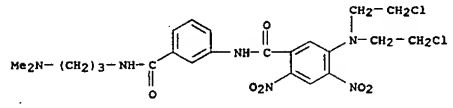
L9 ANSWER 12 OF 47 MEDLINE on STN DUPLICATE 3
(Continued)

L9 ANSWER 13 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:621366 CAPLUS
DOCUMENT NUMBER: 140:283210
TITLE: New carbocyclic lexitropsins with dinitromustard as N-terminal fragment. Inhibition of topoisomerases
AUTHOR(S): Markowska, Agnieszka; Bielawska, Anna; Bielawski, Krzysztof; Midura-Nowaczek, Krystyna
CORPORATE SOURCE: Department of Organic Chemistry, Bialystok, 15-230, Pol.
SOURCE: Acta Poloniae Pharmaceutica (2003), 60(2), 119-121
CODEN: APPHAX; ISSN: 0001-6837
PUBLISHER: Polish Pharmaceutical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of carbocyclic lexitropsins was evaluated for their capacity to inhibit human topoisomerases I and II. The synthesized compds. were carbocyclic oligopeptides with dinitromustard as N-terminal fragment. In the topoisomerases I and II assays, the relaxation of DNA were inhibited with all four compds. This inhibition was directly proportional to the compound concentration

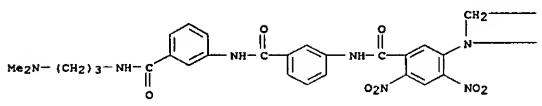
IT 675878-65-6 675878-66-7 675878-67-8
675878-68-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of human topoisomerase I and II by carbocyclic lexitropsins)

RN 675878-65-6 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[3-(dimethylamino)propyl]amino]carbonyl]phenyl]-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 675878-66-7 CAPLUS
CN Benzamide, 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]-N-[3-[[[3-(dimethylamino)propyl]amino]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



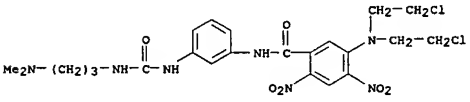
L9 ANSWER 13 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-B

—— CH_2Cl

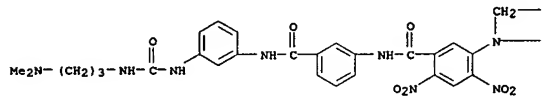
— CH_2— CH_2Cl

RN 675878-67-8 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[[3-(dimethylamino)propyl]amino]carbonyl]amino]phenyl]-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 675878-68-9 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[3-[[[[3-(dimethylamino)propyl]amino]carbonyl]amino]phenyl]amino]carbonyl]phenyl]-2,4-dinitro- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

—— CH_2Cl

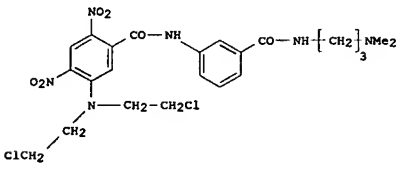
— CH_2— CH_2Cl

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 47 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002157077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11888915
TITLE: Quantitation of bystander effects in nitroreductase suicide gene therapy using three-dimensional cell cultures.
AUTHOR: Wilson William R; Pullen Susan M; Hogg Alison; Helsby Nuala A; Hicks Kevin O; Denny William A
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, Private Bag 92019, Auckland, New Zealand.. wr.wilson@auckland.ac.nz
SOURCE: Cancer research, (2002 Mar 1) Vol. 62, No. 5, pp. 1425-32. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 6 Apr 2002
Entered Medline: 5 Apr 2002

AB The efficacy of cancer gene therapy depends critically on "bystander effects" by which genetic modification of tumor cells results in killing of unmodified cells in the local microenvironment. In gene-dependent enzyme-prodrug therapy, expression of a prodrug-activating suicide gene is used to generate a cytotoxic metabolite that diffuses to nontransduced cells. The objective of this study was to develop a physiologically relevant tissue culture model for quantifying bystander effects and to validate the model using as an example the activation of dinitrobenzamide prodrugs (e.g., CB 1954) by Escherichia coli aerobic nitroreductase (NTR). Bystander effects were measured in three-dimensional multilayer cocultures of NTR+ and NTR- cells by determining clonogenic survival curves for both cell types using V79, Skov3, or WiDr as parental cell lines. Bystander killing by CB 1954 was much more efficient in multilayers than monolayers at equivalent cell:medium ratios, whereas the chloromustard analogue of CB 1954 showed even greater efficiency. For a series of dinitrobenzamides, bystander killing in multilayers showed a positive correlation with prodrug lipophilicity and also correlated with the bystander effect in mixed tumor xenografts grown from the same NTR+ and NTR- WiDr cell lines ($r(2) = 0.84$; $P < 0.001$). The multilayer model identified a bromomustard prodrug (SN 24927) with superior therapeutic activity to CB 1954 that provided curative activity against WiDr tumors comprising 1:1 mixtures of NTR+ and NTR- cells. This study demonstrates the utility of the multilayer tissue culture model for quantifying and optimizing bystander effects in tumors and identifies a new lead prodrug for NTR gene-dependent enzyme-prodrug therapy.

L9 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:931606 CAPLUS
DOCUMENT NUMBER: 139:46376
TITLE: Synthesis and biological activity of carbocyclic lexitropsins with a bioreductive fragment
AUTHOR(S): Markowska, Agnieszka; Rozanski, Andrzej; Wolczynski, Slawomir; Midura-Nowaczek, Krystyna
CORPORATE SOURCE: Department of Organic Chemistry, Medical Academy of Bialystok, Pologne, 15-230, Pol.
SOURCE: Farmaco (2002), 57(12), 1019-1023
CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:46376
GI



I

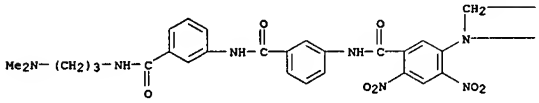
AB Carbocyclic oligopeptides containing two, three or four aromatic rings with N,N-dimethylpropyl-1,3-diamine group as C-terminus fragment and 5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzamide as N-terminal were synthesized. These lexitropsins showed antitumor activity against hepatoblastoma HEP G2. These expts. were evaluated in hypoxic and oxygen conditions. Significant differences of activity in oxygen and hypoxic conditions were shown only for I (IC50=8545 nM in oxygen vs. IC50=710 nM in hypoxia).

IT 343310-44-1P 343310-49-6P 545387-83-5P
545387-86-8P 545387-89-1P 545387-91-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antitumor activity of carbocyclic lexitropsins)

RN 343310-44-1 CAPLUS
CN Benzamide, 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]-N-[3-[[[3-(dimethylamino)propyl]amino]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L9 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



●2 HCl

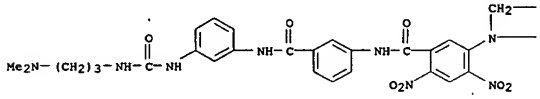
PAGE 1-B

—— CH_2Cl

— CH_2— CH_2Cl

RN 343310-49-6 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[3-[[[[3-(dimethylamino)propyl]amino]carbonyl]amino]phenyl]amino]carbonyl]phenyl]-2,4-dinitro-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



●2 HCl

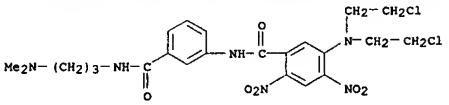
PAGE 1-B

—— CH_2Cl

— CH_2— CH_2Cl

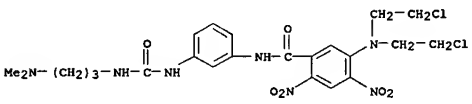
RN 545387-83-5 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[3-(dimethylamino)propyl]amino]carbonyl]phenyl]-2,4-dinitro-, dihydrochloride (9CI) (CA INDEX NAME)

L9 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



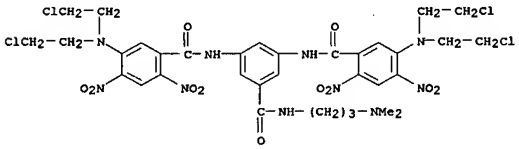
●2 HCl

RN 545387-86-8 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[3-[[[[3-(dimethylamino)propyl]amino]carbonyl]amino]phenyl]-2,4-dinitro-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 545387-89-1 CAPLUS
CN Benzamide, 3,5-bis[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]-N-[3-(dimethylamino)propyl]-, trihydrochloride (9CI) (CA INDEX NAME)



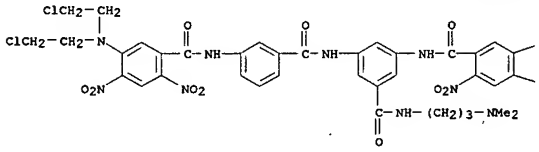
●3 HCl

RN 545387-91-5 CAPLUS

L9 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

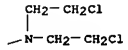
L9 ANSWER 15 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzamide, 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]-5-[[3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]benzoyl]amino]-N-[3-(dimethylamino)propyl]-, trihydrochloride (9CI) (CA INDEX NAME)

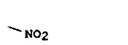
PAGE 1-A



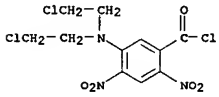
●3 HCl

PAGE 1-B





IT 156423-11-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and antitumor activity of carbocyclic lexitropsins)
RN 156423-11-9 CAPLUS
CN Benzoyl chloride, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS

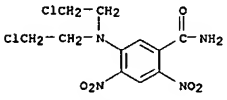
L9 ANSWER 16 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:573922 CAPLUS
DOCUMENT NUMBER: 133:174012
TITLE: Cloning and characterization of microbial nitroreductases and their use for converting CB1954 into anticancer drugs
INVENTOR(S): Minton, Nigel; Anlezark, Gill; Vaughan, Thomas
PATENT ASSIGNEE(S): Microbiological Research Authority, UK
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047725	A1	20000817	WO 2000-GB431	20000210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2362523	A1	20000817	CA 2000-2362523	20000210
EP 1151083	A1	20011107	EP 2000-902770	20000210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002536015	T	20021029	JP 2000-598625	20000210
AU 777860	B2	20041104	AU 2000-24511	20000210
US 2004014191	A1	20040122	US 2003-364397	20030212
PRIORITY APPLN. INFO.:			GB 1999-3019	A 19990210
			WO 2000-GB431	W 20000210
			US 2001-913068	B2 20011228

AB The present invention relates to polypeptides and proteins having nitroreductase activity. The invention also relates to DNA and genes encoding these nitroreductases, and to methods of obtaining such enzymes, DNA and genes. Cloning and sequencing of nitroreductases from Bacillus amyloliquefaciens and B. subtilis is disclosed. Gene and encoded amino acid sequences for a number of microbial nitroreductases are provided. In a particularly preferred aspect, the nitroreductase enzymes demonstrate preferential catalytic conversion of the alkylating agent CB1954 into its highly cytotoxic 4-hydroxylamine (4HX) derivative, this derivative demonstrating anticarcinoma properties. Accordingly, the catalytic activity of the nitroreductase enzymes of the present invention may be employed to achieve catalysis of CB1954 into its cytotoxic derivative in a site-directed manner, such as by Directed-Enzyme Prodrug Therapy (DEPT).
IT 142439-61-0, SN23862
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

L9 ANSWER 16 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
(cloning and characterization of microbial nitroreductases and their use for converting CB1954 or analogs into anticancer drugs)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

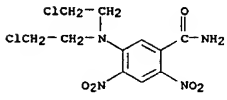
L9 ANSWER 17 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:513828 CAPLUS
DOCUMENT NUMBER: 133:115890
TITLE: Selection of prodrug activating enzyme coding genes using bacteriophage library transformation of lysogenic bacteria
INVENTOR(S): Searle, Peter F.
PATENT ASSIGNEE(S): Cobra Therapeutics Limited, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043541	A1	20000727	WO 2000-GB157	20000121
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358944	A1	20000727	CA 2000-2358944	20000121
EP 1147218	A1	20011024	EP 2000-900727	20000121
EP 1147218	B1	20050316		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 291099	T	20050415	AT 2000-900727	20000121
US 2002123037	A1	20020905	US 2001-889761	20011106

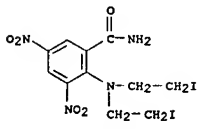
PRIORITY APPLN. INFO.:		
GB 1999-1471	A	19990122
US 1999-116924P	P	19990122
WO 2000-GB157	W	20000121

AB The invention relates to a process for the selection from a gene library of a gene encoding an enzyme that is capable of catalyzing the conversion of a prodrug to its active drug form. The method comprises contacting a library of lysogenic bacteria with a prodrug that causes activation of bacterial RecA when converted to its active drug form. Activation of RecA causes lysis of the bacteria, so allowing separation of bacteriophage particles released into the medium, and their subsequent genotypic anal. to isolate nucleic acid mols. in the library that encode a desired prodrug-activating enzyme.
IT 142439-61-0, SN 23862 188719-25-7
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(prodrug; selection of prodrug activating enzyme coding genes using bacteriophage library transformation of lysogenic bacteria)

L9 ANSWER 17 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



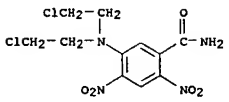
RN 188719-25-7 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L9 ANSWER 18 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:626410 CAPLUS
DOCUMENT NUMBER: 133:204696
TITLE: Crystal structure of FMN-dependent nitroreductase from Escherichia coli B: a prodrug-activating enzyme
AUTHOR(S): Parkinson, Gary N.; Skelly, Jane V.; Neidle, Stephen
CORPORATE SOURCE: CRC Biomolecular Structure Unit Chester Beatty Laboratories, The Institute of Cancer Research, London, SW3 6JB, UK
SOURCE: Journal of Medicinal Chemistry (2000), 43(20), 3624-3631
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The FMN-dependent flavoprotein, nitroreductase (I) from E. coli B is used in cancer chemotherapy to activate a range of prodrugs. Here, the crystal structure of I was determined, using mol. replacement methods and refined at 2.06 Å resolution Recombinant 24-kDa I was crystallized in tetragonal space group P41212, with unit cell dimensions a = b = 57.74 and c = 275.51 Å, and 2 mols. in the asym. unit. The structure had a final R factor of 20.3% (Rfree = 26.7%), for all data between the resolution ranges of 10 and 2.06 Å, and included 4453 protein atoms, 230 water mols., and 2 FMN mols. The functional unit was a homodimer, which formed the asym. unit in the crystal structure. The tertiary structures of these 2 monomers and their subunit interactions were nearly identical. The mol. replacement search model, the crystal structure of the major NAD(P)H-FMN oxidoreductase (II) of Vibrio fischeri, was selected on the basis of its high sequence identity to that of I. The final superposition of these 2 enzymes revealed a very similar overall fold, with variation in the structures focused around surface loops and helixes near the FMN cofactor. Helix G is implicated in substrate specificity and was better resolved in the present I structure than in the previously reported II structure. The FMN-binding pocket was also well-resolved, showing the presence of 2 channels leading into the active site. The amino acid side-chains and main-chain atoms interacting with FMN were well-ordered. The structure of the substrate-binding pocket was used to examine substrate specificity and enzyme kinetics for prodrugs (CB 1954, SN 23862) used in antibody-directed enzyme prodrug therapy (ADEPT) and gene-directed enzyme prodrug therapy (GDEPT).
IT 142439-61-0, SN 23862
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(crystal structure of prodrug-activating FMN-dependent nitroreductase from Escherichia coli B and mol. modeling of prodrug-binding site)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

L9 ANSWER 18 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

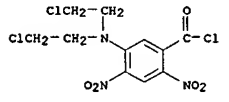
L9 ANSWER 19 OF 47 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001084690 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11127940
TITLE: Pharmacokinetics and metabolism of the nitrogen mustard bioreductive drug 5.
AUTHOR: Kestell P; Pruijn F B; Siim B G; Palmer B D; Wilson W R
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, New Zealand.
SOURCE: Cancer chemotherapy and pharmacology, (2000) Vol. 46, No. 5, pp. 365-74.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 18 Jan 2001

AB PURPOSE: To characterise the pharmacokinetics and metabolism in mice of 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (SN 23862), the lead compound of a new class of bioreductive drugs in which a nitrogen mustard is activated by nitroreduction. Comparison is made with the corresponding aziridine derivative CB 1954. METHODS: Male C3H/HeN mice, bearing s.c. KHT tumours, received 3H-labelled SN 23862 or CB 1954 i.v. at 200 micromol/kg. Plasma, urine and tumour samples were assayed for total radioactivity, and for parent compounds by HPLC. Metabolites were identified by 1H-NMR and mass spectrometry. Cytotoxicity of compounds against Chinese hamster AA8 cells was determined by growth inhibition assay. RESULTS: The plasma pharmacokinetics of SN 23862 and CB 1954 were similar, with half-lives of 1.1 and 1.2 h, respectively. SN 23862 provided tumour/plasma ratios and absolute tumour AUC values almost two times higher than CB 1954. Despite this, SN 23862 was more extensively metabolised than CB 1954, the major route being sequential oxidative dechloroethylation of the nitrogen mustard moiety to the relatively non-toxic half mustard and 5-amine. The inferred chloroacetaldehyde co-product was 260 times more potent than SN 23862. A tetrahydroquinoxaline metabolite resulting from reduction of the 4-nitro group followed by intramolecular alkylation was weakly cytotoxic, while the more cytotoxic 2-amino derivative of SN 23862 was detected in trace amounts. CB 1954 was metabolised by analogous pathways, but the 4- and 2-amine nitroreduction products were the major metabolites while oxidative dealkylation was minor. CONCLUSION: The lesser propensity for SN 23862 to undergo nitroreduction in the host, relative to CB 1954, argues that dinitrobenzamide mustards may be preferable to the corresponding aziridines as bioreductive prodrugs for cancer treatment. However, the toxicological significance of oxidative metabolism of the bis(2-chloroethyl)amine moiety needs to be addressed.

L9 ANSWER 20 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:258356 CAPLUS
DOCUMENT NUMBER: 135:19469
TITLE: Synthetic analogues of netropsin and distamycin. VI. Synthesis of carbocyclic lexitropsins containing a bioreductive element
AUTHOR(S): Markowska, Agnieszka; Rozanski, Andrzej
CORPORATE SOURCE: Department of Organic Chemistry, Medical Academy of Bialystok, Pol.
SOURCE: Acta Poloniae Pharmaceutica (2000), 57(Suppl.), 71-76
CODEN: APPHAX; ISSN: 0001-6837
PUBLISHER: Polish Pharmaceutical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Carbocyclic derivs. of lexitropsins containing two aromatic rings, (dimethylamino)propyl group linked to carboxyl terminus and 5-[bis(2-chloroethyl)-amino]-2,4-dinitrobenzamide group linked to the amino terminus group were synthesized. The N-terminal group should present selective alkylating activity on the DNA of cancer cells in conditions of hypoxia.

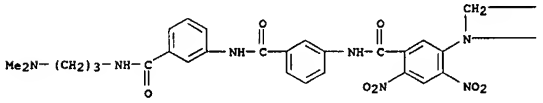
IT 156423-11-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of carbocyclic analogs of lexitropsin antibiotics containing a bioreductive element)
RN 156423-11-9 CAPLUS
CN Benzoyl chloride, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



IT 343310-44-1P 343310-49-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of carbocyclic analogs of lexitropsin antibiotics containing a bioreductive element)
RN 343310-44-1 CAPLUS
CN Benzamide, 3-[[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]-N-[3-[[[3-(dimethylamino)propyl]amino]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L9 ANSWER 20 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



●2 HCl

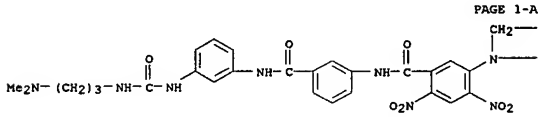
PAGE 1-B

—— CH_2Cl

— CH_2 — CH_2Cl

RN 343310-49-6 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(3-[[[3-[[[[3-(dimethylamino)propyl]amino]carbonyl]amino]phenyl]amino]carbonyl]phenyl]-2,4-dinitro-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



●2 HCl

PAGE 1-B

—— CH_2Cl

— CH_2 — CH_2Cl

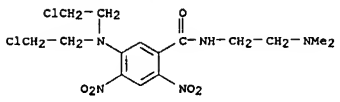
L9 ANSWER 21 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:88266 CAPLUS
DOCUMENT NUMBER: 132:260303
TITLE: Hypoxia-dependent retinal toxicity of bioreductive anticancer prodrugs in mice
AUTHOR(S): Lee, Alan E.; Wilson, William R.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.
SOURCE: Toxicology and Applied Pharmacology (2000), 163(1), 50-59
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bioreductive anticancer prodrug CI-1010 ((2R)-1-{(2-bromoethyl)amino]-3-(2-nitro-1H-imidazol-1-yl)-2-propanol hydrobromide) is an alkylating nitroimidazole which shows selective toxicity against hypoxic cells in murine tumors, but causes extensive apoptosis in the outer retina in rodents and monkeys. This irreversible retinal toxicity has terminated preclin. development of CI-1010. We have investigated whether such toxicity is due to physiol. hypoxia in the retina, and whether it is a general feature of hypoxia-selective bioreductive drugs. Retinal damage was quantified by morphometric anal. of histol. sections following treatment of female C57Bl6 mice. Both CI-1010 and tirapazamine (TPZ, 1,2,4-benzotriazin-3-amine 1,4-dioxide), a bioreductive drug in Phase III clin. trial, caused a time and dose-dependent loss of photoreceptor cells of the outer retina following administration of single i.p. doses. The lesion caused by TPZ was qual. similar to that with CI-1010, but was less severe at equivalent fractions of the maximum tolerated dose (as defined by lethality). With both bioreductive drugs, lesion severity was increased if animals breathed 10% O2 for 3 h after drug administration, while breathing 95% O2/5% CO2 was protective. Other hypoxia-selective bioreductive drugs tested (the quinone porfiromycin, the anthraquinone N-oxide AQ4N and the nitrogen mustard prodrugs SN 23816 and SN 25341) did not cause retinal damage at their maximum tolerated doses. This study suggests that the retinal toxicity of bioreductive drugs might be avoided by manipulation of tissue hypoxia using 95% O2/5% CO2, although this intervention could suppress antitumor activity. The finding that not all bioreductive drugs cause retinal toxicity suggests this toxicity can be avoided through appropriate drug design. (c) 2000 Academic Press.

IT 142439-63-2, SN 23816
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoxia-dependent retinal toxicity of bioreductive anticancer prodrugs in mice)

RN 142439-63-2 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 21 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

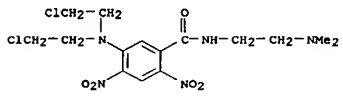
L9 ANSWER 22 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:96379 CAPLUS
DOCUMENT NUMBER: 130:163172
TITLE: Methods of using cytochrome P450 reductase for the enhancement of P450-based anticancer gene therapy
INVENTOR(S): Waxman, David J.; Chen, Ling
PATENT ASSIGNEE(S): Trustees of Boston University, USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905299	A1	19990204	WO 1998-US15302	19980723
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6207648	B1	20010327	US 1998-118179	19980717
AU 9887578	A	19990216	AU 1998-87578	19980723
EP 1017835	A1	20000712	EP 1998-939083	19980723
R: DE, DK, ES, FR, GB, IT				
JP 2003524367	T	20030819	JP 2000-504269	19980723
PRIORITY APPLN. INFO.:			US 1997-53677P P	19970724
			US 1998-118179 A	19980717
			WO 1998-US15302 W	19980723

AB Methods of killing neoplastic cells are provided. The invention relates to the use of NADPH-cytochrome P 450 reductase (RED) gene transfer in combination with cytochrome P 450 gene transfer to enhance the sensitivity of tumor cells to anticancer drugs that are activated by P 450 enzymes. The use of bioreductive drugs that are activated by RED and/or cytochrome P 450, in this paradigm, is also provided.

IT 142439-63-2, NSC 646394
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of using cytochrome P 450 reductase for the enhancement of P 450-based anticancer gene therapy)

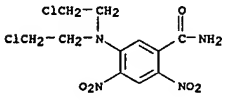
RN 142439-63-2 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L9 ANSWER 23 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:691450 CAPLUS
DOCUMENT NUMBER: 132:73319
TITLE: Role of redox cycling and activation by DT-diaphorase in the cytotoxicity of 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB-1954) and its analogs
AUTHOR(S): Miskiniene, V.; Sergediene, E.; Nemeikaite, A.; Segura-Aguilar, J.; Cenas, N.
CORPORATE SOURCE: Institute of Biochemistry, Vilnius, Lithuania
SOURCE: Cancer Letters (Shannon, Ireland) (1999), 146(2), 217-222
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In tumor cell lines with high content of DT-diaphorase (EC 1.6.99.2), the cytotoxicity of 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB-1954) and its derivs. is exerted through DT-diaphorase-catalyzed formation of crosslinking species. However, little is known about other possible mechanisms of CB-1954 action. We have examined the toxicity of CB-1954 and its derivs. to bovine leukemia virus-transformed lamb fibroblasts (line FLK), which possessed moderate DT-diaphorase activity, 260 units/mg protein. The action of these compds. was accompanied by lipid peroxidn., their toxicity was decreased by desferrioxamine and antioxidant N,N'-diphenyl-p-phenylene diamine (DPPD), but, in most cases, not by dicumarol, an inhibitor of DT-diaphorase. Using multiparameter regression anal., we have found that the toxicity of CB-1954 derivs. as well as that of several non-alkylating nitroaroms., increased upon the increase in their single-electron reduction potential (E17) and octanol/water partition coefficient (P), and almost did not depend on their reactivity towards DT-diaphorase. It seems that in cell lines with a moderate amount of DT-diaphorase, the toxicity of CB-1954 and its analogs is exerted through their redox cycling.
IT 142439-61-0, SN 23862
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(role of redox cycling and activation by DT-diaphorase in the cytotoxicity of CB-1954 and its analogs)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



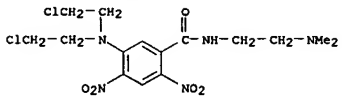
L9 ANSWER 23 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 47 MEDLINE on STN
ACCESSION NUMBER: 1999090112 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9873426
TITLE: Synthesis and hypoxia-selective cytotoxicity of a 2-nitroimidazole mustard.
AUTHOR: Lee H H; Palmer B D; Wilson W R; Denny W A
CORPORATE SOURCE: Auckland Cancer Society Research Centre, New Zealand.
CONTRACT NUMBER: N01-CM 47019 (NCI)
SOURCE: Bioorganic & medicinal chemistry letters, (1998 Jul 7) Vol. 8, No. 13, pp. 1741-4.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 16 Feb 1999
Last Updated on STN: 16 Feb 1999
Entered Medline: 29 Jan 1999
AB A four-step synthesis of 5-[N,N-bis(2-chloroethyl)amino]-1-methyl-2-nitroimidazole from 1-methyl-2-nitroimidazole is described. This compound showed similar hypoxia-selective cytotoxicity to the dinitrobenzamide mustard SN 23,862 in UV4 cells (ca. 40-fold), and superior selectivity (> 7-fold) in repair-competent AA8 cells.

L9 ANSWER 25 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:571075 CAPLUS
DOCUMENT NUMBER: 129:310544
TITLE: Enhancement of the anti-tumor effects of the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) by combination with 5-hydroxytryptamine and bioreductive drugs
AUTHOR(S): Lash, C. J.; Li, A. E.; Rutland, M.; Baguley, B. C.; Zwi, L. J.; Wilson, W. R.
CORPORATE SOURCE: Section of Oncology, Department of Pathology, The University of Auckland, Auckland, N. Z.
SOURCE: British Journal of Cancer (1998), 78(4), 439-445
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The tumor blood flow inhibitor 5,6-dimethylxanthenone-4-acetic acid (DMXAA) causes dramatic hemorrhagic necrosis in murine tumors, but activity is seen only at doses close to the toxic limit. This study investigates two approaches for increasing the therapeutic ratio of DMXAA.
The first approach combines DMXAA with a second tumor blood flow inhibitor, 5-hydroxytryptamine (5-HT). Co-administration of 5-HT (700 μmol kg-1) to C3H mice caused marked enhancement of DMXAA effects against MDAH-MCa-4 tumors, with dose-modifying factors (DMFs) of >3 for blood flow inhibition (at 4 h), 2.3 for necrosis (at 12 h) and 2.0 for growth delay, without compromising the maximum tolerated dose of DMXAA (90 μmol kg-1). The data are consistent with ischemic injury to the tumor being the major mechanism of antitumor activity. The second approach combines DMXAA (± 5-HT) with hypoxia-selective bioreductive drugs. Anti-tumor activity of all three bioreductive drugs tested (tirapazamine, CI-1010, SN 23816) was strongly potentiated by DMXAA, suggesting that there is a population of reversibly hypoxic tumor cells after DMXAA treatment. Co-administration of 5-HT further potentiated anti-tumor activity, but also increased host toxicity of tirapazamine and CI-1010 so that little therapeutic benefit was achieved. In contrast, the host toxicity of the dinitrobenzamide mustard SN 23816 was only slightly increased by DMXAA/5-HT, whereas the tumor growth delay at the maximum tolerated dose of SN 23816 was increased from 3.5 to 26.5 days. This study demonstrates that 5-HT and/or bioreductive drugs can improve the therapeutic activity of DMXAA in mice, and that with SN 23816 both approaches can be used together to provide considerably enhanced anti-tumor activity.
IT 142439-63-2, SN 23816
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(enhancement of antitumor effects of antivascular agent 5,6-dimethylxanthenone-4-acetic acid by combination with 5-hydroxytryptamine and bioreductive drugs)
RN 142439-63-2 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 25 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L9 ANSWER 26 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:499055 CAPLUS
DOCUMENT NUMBER: 127:140542
TITLE: Targeted cytotoxic prodrugs
INVENTOR(S): Bagshawe, Kenneth Dawson; Burke, Philip John
PATENT ASSIGNEE(S): Aepact Ltd., UK
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9724143	A1	19970710	WO 1996-GB3254	19961227
W: GB, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2168680	A1	19970630	CA 1996-2168680	19960202
EP 869818	A1	19981014	EP 1996-944114	19961227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000502698	T	20000307	JP 1997-524114	19961227
US 2002131973	A1	20020919	US 1998-91933	19981210
US 2004037835	A1	20040226	US 2003-614603	20030707

PRIORITY APPLN. INFO.:

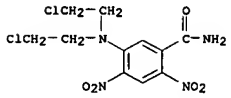
US 1995-9361P	P	19951229
CA 1996-2168680	A	19960202
WO 1996-GB3254	W	19961227
US 1998-91933	B1	19981210

AB A therapeutic system for destroying a target cell within a host having a vascular compartment, the system comprising: (a) a compound comprising a target cell-specific portion and a portion which will convert a selected substantially non-cytotoxic substance into a cytotoxic substance; and (b) said substantially non-cytotoxic substance, wherein at least the said portion of compound (a) capable of said conversion is, following administration to the host, internalized into said target cell. Preferably, the portion which converts said substantially non-cytotoxic substance into a cytotoxic substance requires a factor which is present in sufficient concentration within the target cell for the said portion to effect conversion of said substantially non-cytotoxic substance into a cytotoxic substance and which factor is not present in sufficient concentration within the blood of the vascular compartment for the said portion to effect said conversion.

IT 142439-61-0, SN 23862
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(targeted cytotoxic prodrugs)

RN 142439-61-0 CAPLUS

L9 ANSWER 26 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

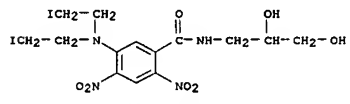


L9 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:198120 CAPLUS
DOCUMENT NUMBER: 126:246358
TITLE: Mustard Prodrugs for Activation by Escherichia coli Nitroreductase in Gene-Directed Enzyme Prodrug Therapy
AUTHOR(S): Friedlos, Frank; Denny, William A.; Palmer, Brian D.; Springer, Caroline J.
CORPORATE SOURCE: Cancer Research Campaign Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton / Surrey, SM2 5NG U.K., UK
SOURCE: Journal of Medicinal Chemistry (1997), 40(8), 1270-1275
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Twenty nitrogen mustard analogs derived from 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB 1954) were evaluated as candidate prodrugs for gene-directed enzyme prodrug therapy (GDEPT) in Chinese hamster V79 cell lines engineered to express Escherichia coli nitroreductase (NR). Structural variations within the series included the use of N-dihydroxypropyl and (N-dimethylamino)ethyl carboxamide side chains, the use of chloro, bromo, mesyl, and iodo leaving groups on the mustards, and regioisomeric changes. The compds. were assayed for cytotoxicity (IC) with the NR-expressing and controls of non-NR-expressing cell lines. The proportion of NR-expressing cells required in a mixture for nonexpressing cells to experience 50% of their cytotoxicity (termed the TE50) was used to assess the compds.' ability to induce a bystander effect. This study suggests that 5-[N,N-bis(2-bromoethyl)amino]-2,4-dinitrobenzamide, 5-[N,N-bis(2-iodoethyl)amino]-2,4-dinitrobenzamide, 2-[N,N-bis(2-bromoethyl)amino]-3,5-dinitrobenzamide, and 2-[N,N-bis(2-iodoethyl)amino]-3,5-dinitrobenzamide showed considerable improvements over CB 1954, exhibiting higher potency, higher IC50 ratios, and lower TE50s, and are thus superior prodrugs to CB 1954 for GDEPT.

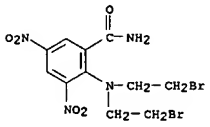
IT 188719-22-4P 188719-23-5P 188719-25-7P 188719-28-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and structure activity of aziridinyl mustard prodrugs for activation by Escherichia coli nitroreductase in gene-directed enzyme prodrug therapy)

RN 188719-22-4 CAPLUS
CN Benzamide, 5-[bis(2-iodoethyl)amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

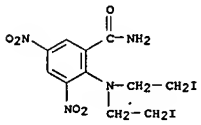


RN 188719-23-5 CAPLUS

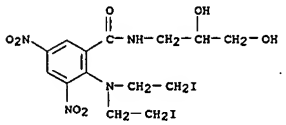
L9 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzamide, 2-[bis(2-bromoethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 188719-25-7 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)

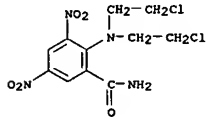


RN 188719-28-0 CAPLUS
CN Benzamide, 2-[bis(2-iodoethyl)amino]-N-(2,3-dihydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

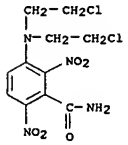


IT 142439-61-0 150271-87-7 150271-88-8
150272-00-7 150272-02-9 150272-04-1
150272-05-2 169527-44-0 185946-02-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(preparation and structure activity of aziridinyl mustard prodrugs for activation by Escherichia coli nitroreductase in gene-directed enzyme

L9 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 150272-02-9 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)



RN 150272-04-1 CAPLUS
CN Benzamide, 3-[bis(2-chloroethyl)amino]-2,6-dinitro- (9CI) (CA INDEX NAME)



RN 150272-05-2 CAPLUS
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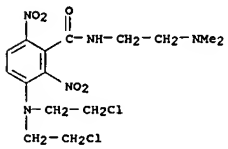
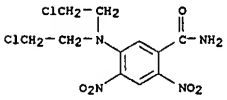
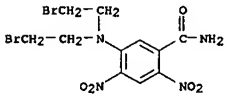


RN 169527-44-0 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-(2,3-dihydroxypropyl)-3,5-dinitro- (9CI) (CA INDEX NAME)

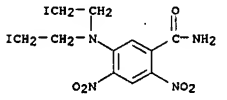
L9 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
prodrug therapy)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



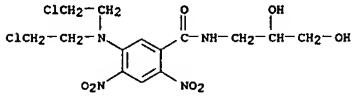
RN 150271-87-7 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



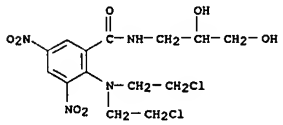
RN 150271-88-8 CAPLUS
CN Benzamide, 5-[bis(2-iodoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)



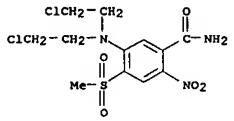
RN 150272-00-7 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



L9 ANSWER 27 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 185946-02-5 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-4-(methylsulfonyl)-2-nitro- (9CI) (CA INDEX NAME)



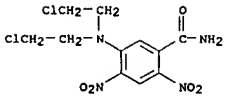
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:425415 CAPLUS
DOCUMENT NUMBER: 125:76329
TITLE: Transgenic nonhuman animals expressing nitroreductase which converts prodrug to cytotoxic drug
INVENTOR(S): Clark, John; Connors, Thomas; Gusterson, Barry; Knox, Richard
PATENT ASSIGNEE(S): Cancer Research Campaign Technology Limited, UK; Agricultural and Food Research Council
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9614420	A1	19960517	WO 1995-GB2596	19951106
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9538123	A	19960531	AU 1995-38123	19951106
PRIORITY APPLN. INFO.:			GB 1994-22264 A	19941104
			WO 1995-GB2596 W	19951106

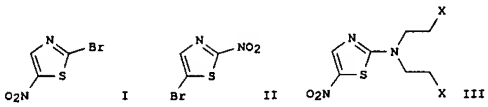
AB The present invention provides a method of producing a transgenic non-human animal, which method comprises incorporating into the genome of the non-human animal at least one nucleotide sequence comprising a sequence encoding a nitroreductase which is capable of converting a prodrug into a cytotoxic drug. Plasmids containing Escherichia coli nitroreductase under control of the sheep β-lactoglobulin promoter were constructed and transgenic mice expressing this chimeric gene were prepared Mammary cell ablation was achieved by injection of prodrug CB 1954
[5-(aziridin-1-yl)-2,4-dinitrobenzamide].
IT 142439-61-0, SN 23862
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transgenic nonhuman animals expressing nitroreductase which converts prodrug to cytotoxic drug)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

L9 ANSWER 28 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



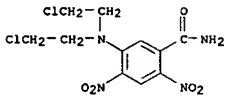
L9 ANSWER 29 OF 47 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 96265151 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8691449
TITLE: Hypoxia-selective antitumor agents. 14. Synthesis and hypoxic cell cytotoxicity of regioisomers of the hypoxia-selective cytotoxin 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide.
AUTHOR: Palmer B D; Wilson W R; Anderson R F; Boyd M; Denny W A
CORPORATE SOURCE: Department of Pathology, University of Auckland School of Medicine, New Zealand.
CONTRACT NUMBER: N0-1 CM 47019 (NCI)
SOURCE: Journal of medicinal chemistry, (1996 Jun 21) Vol. 39, No. 13, pp. 2518-28.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 11 Sep 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 23 Aug 1996
AB A series of regioisomers of the novel hypoxia-selective cytotoxin (HSC) 5-[N,N-bis(2-chloroethyl)-amino]-2,4-dinitrobenzamide (2a) have been prepared by displacement of the chloro group from methyl chlorodinitrobenzoates or the corresponding carboxamides with diethanolamine, followed by dimesylation and mesylate displacement with LiCl. The compounds fall into two classes, where the two nitro groups have either a meta or an ortho (or para) disposition to each other. The four meta derivatives had one-electron reduction potentials in the range -340 to -375 mV, similar to that of the known isomer 2a, while the other isomers had much higher values (-262 to -285 mV). The meta derivatives were much less cytotoxic to AA8 cells under aerobic conditions (IC50s from 75 to 470 microM) than were the other compounds (IC50s from 1.6 to 20 microM). However, the ratios of IC50s of the compounds in repair-proficient (AA8) and repair-deficient (UV4) cell lines varied, indicating differing contributions of DNA alkylation to aerobic toxicity between the isomers, with no clear relationship between this and nitro group disposition. The hypoxic selectivities of the (dimethylamino)ethylcarboxamide analogues for each isomer were determined by clonogenic assay against both AA8 and UV4 cells. With one exception, the meta derivatives showed excellent hypoxic selectivities (ca. 45-115-fold) against UV4 cells, while the ortho or para isomers had little selectivity (ca. 2-7-fold). A possible reason may be that the latter compounds, with higher reduction potentials, undergo rapid bioreduction even under aerobic conditions. None showed hypoxic selectivities greater than 2-3-fold against AA8 cells. The 3-[N,N-bis(2-chloroethyl)amino]-2,6-dinitrobenzamide isomer (5b), which showed the highest hypoxic selectivity for UV4 cells in this series, was active against both hypoxic and aerobic cells in KHT tumors in mice at well-tolerated doses, and showed superior in vivo activity to the previously studied 2,4-dinitro isomer 2b.

L9 ANSWER 30 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:582744 CAPLUS
DOCUMENT NUMBER: 125:300879
TITLE: Unexpected rearrangement products from aminations of 5-bromo-2-nitrothiazole
AUTHOR(S): Lee, Ho H.; Palmer, Brian D.; Boyd, Maruta; Denny, William A.
CORPORATE SOURCE: Cancer Res. Lab., Univ. Auckland Sch. Med., Auckland, 92019, N. Z.
SOURCE: Journal of Heterocyclic Chemistry (1996), 33(4), 1191-1194
CODEN: JHTCAD; ISSN: 0022-152X
PUBLISHER: HeteroCorporation
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 125:300879
GI



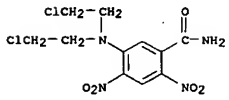
AB Whereas reaction of 2-bromo-5-nitrothiazole (I) with weakly nucleophilic secondary aliphatic amines (such as diethanolamine) gives the expected 2-amino products from nucleophilic displacement of Br, reaction of isomeric 5-bromo-2-nitrothiazole (II) with such amines gives mixts. of the expected 5-amino products together with 2-aminated 5-nitrothiazole rearrangement products such as III [X = OH]. The identities of the abnormal products were determined by alternative synthesis, and by x-ray crystallog. determination of the derived mustard III [X = Cl]. The mechanism proposed is a slow thermal isomerization of II to the much more reactive I, which competes, in the case of relatively weak amine nucleophiles, with the normal and direct (but slow) nucleophilic displacement of the 5-Br atom.
IT 142439-61-0DP, 5-[N,N-Bis(2-chloroethyl)amino]-2,4-dinitrobenzamide, heterocyclic analogs
RL: SPN (Synthetic preparation); PREP (Preparation)
(aminations of isomeric bromonitrothiazoles with unexpected rearrangement of 5-bromo-2-nitro isomer)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

L9 ANSWER 30 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L9 ANSWER 31 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:706671 CAPLUS
DOCUMENT NUMBER: 126:98829
TITLE: Synthesis and evaluation of 4-substituted analogs of 5-[N,N-bis(2-chloroethyl)amino]-2-nitrobenzamide as bioreductively activated prodrugs using an Escherichia coli nitroreductase
AUTHOR(S): Atwell, Graham J.; Boyd, Maruta; Palmer, Brian D.; Anderson, Robert F.; Pullen, Susan M.; Wilson, William R.; Denny, William A.
CORPORATE SOURCE: Cancer Societyy Res. Lab., Fac. Med. and Healthh Sci, Univ. Auckland, Auckland, 92019, N. Z.
SOURCE: Anti-Cancer Drug Design (1996), 11(7), 553-567
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2,4-Dinitrobenzamide mustards, exemplified by the parent compound SN 23862 (I) are activated under aerobic conditions by an Escherichia coli nitroreductase enzyme (NR2) via selective reduction of the 2-nitro group, and are thus of interest as prodrugs for antibody-directed enzyme-prodrug therapy (ADEPT). A series of related compds. where the 4-nitro group of I was replaced by other substituents of varying electronic properties, were prepared and evaluated as potential ADEPT prodrugs. One-electron reduction potentials of the compds. correlated well with the substituent σm values, with the exception of the unsubstituted analog, which had a much lower value than expected on electronic grounds, due to a coplanar conformation of the mustard. The cytotoxicities of the compds. towards aerobic UV4 cells correlated pos. with the electron-donating ability of the 4-substituent (measured by σp values), indicating that the cytotoxicities of the compds. in the absence of the NR2 enzyme are due substantially to the parent (unreduced) compds. A pos., although less strong, correlation was seen between the electronic properties of the 4-substituent and their cytotoxicities in the presence of the NR2 enzyme, suggesting that, in this closely related series, the degree of activation by the enzyme is significantly dependent on the reduction potential of the 2-nitro group. While the 4-SO2Me derivative was the next most preferred substrate after the parent I, it was considerably less so (degree of activation as measured by IC50 ratio of 26 compared with 145), despite the similar electronic properties of the two 4-substituents.
IT 142439-61-0, SN 23862
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and evaluation of substituted analogs of [bis(chloroethyl)amino]nitrobenzamide as bioreductively activated prodrugs using an Escherichia coli nitroreductase)
RN 142439-61-0 CAPLUS

L9 ANSWER 31 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

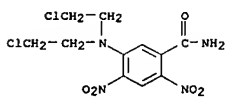


IT 185946-02-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and evaluation of substituted analogs of [bis(chloroethyl)amino]nitrobenzamide as bioreductively activated prodrugs using an Escherichia coli nitroreductase)
RN 185946-02-5 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-4-(methylsulfonyl)-2-nitro- (9CI) (CA INDEX NAME)

L9 ANSWER 32 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:735514 CAPLUS
DOCUMENT NUMBER: 123:132855
TITLE: Improvements relating to cancer therapy
INVENTOR(S): Connors, Thomas; Knox, Richard; Sherwood, Roger
PATENT ASSIGNEE(S): Cancer Research Campaign Technology Ltd., UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9512678	A2	19950511	WO 1994-GB2423	19941104
WO 9512678	A3	19950615		
W: AU, CA, JP, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2175687	A1	19950511	CA 1994-2175687	19941104
CA 2175687	C	20060509		
AU 9480657	A	19950523	AU 1994-80657	19941104
AU 690935	B2	19980507		
EP 725826	A1	19960814	EP 1994-931658	19941104
EP 725826	B1	20050126		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09505037	T	19970520	JP 1995-513099	19941104
JP 3867211	B2	20070110		
AT 287958	T	20050215	AT 1994-931658	19941104
ES 2237754	T3	20050801	ES 1994-931658	19941104
US 5958682	A	19990928	US 1996-640808	19960701
PRIORITY APPLN. INFO.:			GB 1993-23008 A	19931105
			WO 1994-GB2423 W	19941104

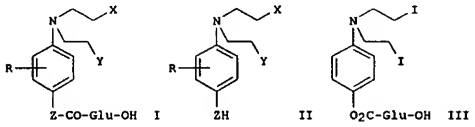
AB The system of the invention comprises: (i) a viral vector comprising a nucleotide sequence encoding a nitroreductase, which nitroreductase is capable of converting a prodrug into a cytotoxic drug and (ii) a prodrug, e.g. nitrogen mustard, capable of being converted into a cytotoxic drug by the nitroreductase encoded by the vector. The gene encoding nitroreductase of Escherichia coli is cloned and its use in combination with prodrugs (e.g. CB 1954 and SN23865) demonstrated.
IT 142439-61-0, SN 23862
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug; cancer therapy using viral vector expressing gene for nitroreductase of Escherichia coli and)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)



L9 ANSWER 32 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L9 ANSWER 33 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN

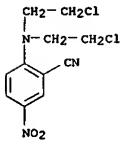
ACCESSION NUMBER: 1995:965043 CAPLUS
DOCUMENT NUMBER: 124:117909
TITLE: Optimization of Alkylating Agent Prodrugs Derived from Phenol and Aniline Mustards: A New Clinical Candidate Prodrug (ZD2767) for Antibody-Directed Enzyme Prodrug Therapy
AUTHOR(S): Springer, Caroline J.; Dowell, Robert; Burke, Philip J.; Hadley, Elma; Davies, D. Huw; Blakey, David C.; Melton, Roger G.; Niculescu-Duvaz, Ion
CORPORATE SOURCE: Cancer Research Campaign Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, SM2 5NG, UK
SOURCE: Journal of Medicinal Chemistry (1995), 38(26), 5051-65
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Sixteen novel potential prodrugs I [R = H, 2-Me, 2-Cl, 3-Me, 3-Me2CH, 3-F, 2,3-(CH:CHCH:CH), 3-CN; Z = O, NH; X, Y = Cl, Br, iodo, O3SMe] derived from phenol or aniline mustards and their 16 corresponding drugs II with ring substitution and/or different alkylating functionalities were designed. They are bifunctional alkylating agents in which the activating effect of the phenolic hydroxyl or amino function is masked through an oxycarbonyl or a carbamoyl bond to a glutamic acid. These prodrugs were designed to be activated to their corresponding phenol and aniline nitrogen mustard drugs at a tumor site by prior administration of a monoclonal antibody conjugated to the bacterial enzyme carboxypeptidase G2 (CPG2) in antibody-directed enzyme prodrug therapy (ADEPT). The synthesis of the analogous novel parent drugs II is also described. The viability of a colorectal cell line (LoVo) was monitored with the potential prodrugs and the parent drugs. The differential in the cytotoxicity between the potential prodrugs and their corresponding active drugs ranged between 12 and >195 fold. Some compds. I exhibited substantial prodrug activity, since a cytotoxicity differential of >100 was achieved compared to the analogous II. The ability of the potential prodrugs to act as substrates for CPG2 was detd. (kinetic parameters KM and kcat), and the chem. stability was measured for all the compds. The unsubstituted phenols with different alkylating functionalities (I; R = H, Z = O) proved to have the highest ratio of substrates kcat:KM. From these studies, III (ZD2767) emerges as a new ADEPT clin. trial candidate due to its physicochem. and biol. characteristics.

L9 ANSWER 33 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

IT 156079-60-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(optimization of alkylating agent prodrugs derived from phenol and aniline mustards in preparation of prodrug ZD2767 for antibody-directed enzyme prodrug therapy)
RN 156079-60-6 CAPLUS
CN Benzonitrile, 2-[bis(2-chloroethyl)amino]-5-nitro- (9CI) (CA INDEX NAME)



L9 ANSWER 34 OF 47 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 95222533 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7707325
TITLE: Reductive chemistry of the novel hypoxia-selective cytotoxin 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide.
AUTHOR: Palmer B D; van Zijl P; Denny W A; Wilson W R
CORPORATE SOURCE: Cancer Research Laboratory, University of Auckland School of Medicine, New Zealand.
CONTRACT NUMBER: CM 47019 (NCI)
SOURCE: Journal of medicinal chemistry, (1995 Mar 31) Vol. 38, No. 7, pp. 1229-41.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 18 May 1995
Last Updated on STN: 18 May 1995
Entered Medline: 11 May 1995

AB 5-[N,N-Bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (1; SN 23862) is a novel bioreductive drug whose selective toxicity for hypoxic cells appears due to oxygen-inhibited enzymatic reduction of one of the nitro groups to the corresponding amine or hydroxylamine. Radiolytic reduction of 1 using up to four reducing equivalents in 1 N sodium formate was shown to proceed via electron addition to the 4-nitro group, thereby identifying this substituent as the most electron-affinic site in the molecule. The initially-formed 4-hydroxylamine and its N-hydroxytetrahydroquinoxaline half-mustard cyclization product (formed by intramolecular reaction with one arm of the adjacent mustard group) are reduced to the corresponding 4-amines upon further addition of electrons, although reduction of the 2-nitro group leading to 2,4-diamino products begins after addition of only six electron equivalents. Radiolytic reduction of the structurally similar 5-(aziridin-1-yl)-2,4-dinitrobenzamide (2; CB 1954) with six electron equivalents also occurs at the 4-nitro group to give the 4-hydroxylamine and 4-amine. The product mixture from reduction of 2 is less complex, largely because the corresponding 4-hydroxylamine and 4-amine are stable. The major reduction products of 1 were chemically synthesized by unequivocal routes to provide authentic samples for identification of the products of radiolytic reduction and to allow determination of their cytotoxicities. The 2- and 4-amino derivatives of 1 are significantly more cytotoxic than the parent drug, although the toxicity of the 4-amine is moderated by its facile conversion to the corresponding less toxic tetrahydroquinoxaline half-mustard. Although the 2- and 4-hydroxylamino derivatives were prepared by chemical reduction of 1, their toxicity could not be evaluated because of their instability. The 4-hydroxylamine reacts intramolecularly with the 5-mustard group somewhat more rapidly than does the 4-amine, while the 2-hydroxylamine is converted into a 2,2'-azoxy dimer following aerial oxidation to the 2-nitroso derivative. The fully reduced 2,4-diamino derivative of 1 is 10-fold more cytotoxic again than the 2-amine and, surprisingly, does not undergo spontaneous intramolecular alkylation. This elucidation of the

L9 ANSWER 34 OF 47 MEDLINE on STN DUPLICATE 7
(Continued)
reduction chemistry of 1 will facilitate further investigations of the toxic products generated from this compound both by hypoxic tumor cells and by ADEPT enzymes.

L9 ANSWER 35 OF 47 MEDLINE on STN
ACCESSION NUMBER: 96167006 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8593750
TITLE: Hypoxia-activated prodrugs as antitumour agents: strategies for maximizing tumour cell killing.
AUTHOR: Wilson W R; Pruijn F B
CORPORATE SOURCE: Department of Pathology, University of Auckland School of Medicine, New Zealand.
SOURCE: Clinical and experimental pharmacology & physiology, (1995 Nov) Vol. 22, No. 11, pp. 881-5.
Journal code: 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 22 Apr 1996
Last Updated on STN: 22 Apr 1996
Entered Medline: 9 Apr 1996
AB 1. Hypoxia arises in solid tumour because of inefficient blood supply. While hypoxic cells are resistant to radiotherapy and probably to many chemotherapeutic drugs they can, in principle, be turned to advantage through the development of hypoxia-activated cytotoxic drugs (bioreductive drugs). 2. Three general approaches to exploiting tumour hypoxia are discussed. The first relies on fluctuating blood flow in tumours and the consequent cycling of cells through the hypoxic compartment. The second incorporates a prodrug approach in which drug activation gives rise to cytotoxic metabolites which diffuse out of hypoxic zones. The third utilizes selective inhibitors of tumour blood flow to induce additional hypoxia and thus enhance bioreductive drug activation. 3. The latter two approaches are illustrated by recent studies with the dinitrobenzamide nitrogen mustard class of bioreductive drugs and their combination with the tumour blood flow inhibitor 5,6-dimethylxanthenone-4-acetic acid.

L9 ANSWER 36 OF 47 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 95398664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7669063
TITLE: Bioactivation of dinitrobenzamide mustards by an E. coli B nitroreductase.
AUTHOR: Anlezark G M; Melton R G; Sherwood R F; Wilson W R; Denny W A; Palmer B D; Knox R J; Friedlos F; Williams A
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wilts, U.K.
SOURCE: Biochemical pharmacology, (1995 Aug 25) Vol. 50, No. 5, pp. 609-18.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 20 Oct 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 12 Oct 1995
AB A nitroreductase isolated and purified from Escherichia coli B has been demonstrated to have potential applications in ADEPT (antibody-directed enzyme prodrug therapy) by its ability in vitro to reduce dinitrobenzamides (e.g. 5-aziridinyl 2,4-dinitrobenzamide, CB 1954 and its bischloroethylamino analogue, SN 23862) to form cytotoxic derivatives. In contrast to CB 1954, in which either nitro group is reducible to the corresponding hydroxylamine, SN 23862 is reduced by the nitroreductase to form only the 2-hydroxylamine. This hydroxylamine can react with S-acetylthiocholine to form a species capable of producing interstrand crosslinks in naked DNA. In terms of ADEPT, SN 23862 has a potential advantage over CB 1954 in that it is not reduced by mammalian DT diaphorases. Therefore, a series of compounds related to SN 23862 has been synthesized, and evaluated as potential prodrugs both by determination of kinetic parameters and by ratio of IC50 against UV4 cells when incubated in the presence of prodrug, with and without the E. coli enzyme and cofactor (NADH). Results from the two studies were generally in good agreement in that compounds showing no increase in cytotoxicity in presence of enzyme and cofactor were not substrates for the enzyme. None of the analogues were activated by DT diaphorase isolated from Walker 256 carcinoma cells. For those compounds which were substrates for the E. coli nitroreductase, there was a positive correlation between kcat and IC50 ratio. Two compounds showed advantageous properties: SN 25261 (with a dihydroxypropylcarboxamide ring substituent) which has a more than 10-fold greater aqueous solubility than SN 23862 whilst retaining similar kinetic characteristics and cytotoxic potency; and SN 25084, where a change in the position of the carboxamide group relative to the mustard resulted in an increased cytotoxicity ratio and kcat compared with SN 23862 (IC50 ratios 214 and 135; kcat values of 75 and 26.4 sec-1, respectively). An analogue (SN 25507) incorporating both these structural changes had an enhanced kcat of 576 sec-1. This study elucidates some of the structural requirements of the enzyme and aids identification of further directions in the search for suitable prodrugs for an ADEPT

L9 ANSWER 36 OF 47 MEDLINE on STN DUPLICATE 8
(Continued)
nitroreductase system.

L9 ANSWER 37 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:482718 CAPLUS
DOCUMENT NUMBER: 121:82718
TITLE: Amino acid-linked nitrogen mustard derivatives and their use as carboxypeptidase G2-activated prodrugs in the treatment of tumors
INVENTOR(S): Burke, Philip John; Dowell, Robert Ian; Mauger, Anthony Brian; Springer, Caroline Joy
PATENT ASSIGNEE(S): Zeneca Ltd., UK; Cancer Research Campaign Technology Ltd.
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9402450	A1	19940203	WO 1993-GB1560	19930723
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9305290	A	19940426	ZA 1993-5290	19930721
CA 2101104	A1	19940124	CA 1993-2101104	19930722
CA 2101104	C	20070123		
US 5405990	A	19950411	US 1993-94952	19930722
IL 106459	A	19980208	IL 1993-106459	19930722
AU 9347156	A	19940214	AU 1993-47156	19930723
AU 681349	B2	19970828		
EP 651740	A1	19950510	EP 1993-917904	19930723
EP 651740	B1	19981021		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 69288	A2	19950928	HU 1995-145	19930723
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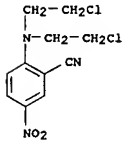
JP 3541037	B2	20040707		
PL 174617	B1	19980831	PL 1993-307226	19930723
AT 172450	T	19981115	AT 1993-917904	19930723
ES 2123662	T3	19990116	ES 1993-917904	19930723
RU 2129542	C1	19990427	RU 1995-105246	19930723
CZ 287028	B6	20000816	CZ 1995-151	19930723
SK 281338	B6	20010212	SK 1995-69	19930723
US 5587161	A	19961224	US 1994-361424	19941221
FI 9500230	A	19950119	FI 1995-230	19950119
FI 115048	B1	20050228		
NO 9500210	A	19950123	NO 1995-210	19950120
US 5660829	A	19970826	US 1995-442348	19950516
US 5714148	A	19980203	US 1996-722669	19960930
US 5958971	A	19990928	US 1997-956008	19971022
US 6277880	B1	20010821	US 1999-314894	19990519
PRIORITY APPLN. INFO.:			GB 1992-15636 A	19920723

L9 ANSWER 37 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



L9 ANSWER 37 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

	GB 1993-10884	A 19930526
	US 1993-94952	A3 19930722
	WO 1993-GB1560	W 19930723
	US 1994-361424	A1 19941221
	US 1996-722669	A1 19960930
	US 1997-956008	A1 19971022

OTHER SOURCE(S): MARPAT 121:82718
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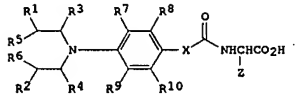

I

AB The title compound [I; R1, R2 = Cl, Br, iodo, OSO2Me, (un)substituted OSO2Ph; R3-R6 = H, C1-4 alkyl, C1-4 haloalkyl; R7-R10 = H, (un)substituted C1-4 alkyl, etc.; X = O, NH, CH2; Z = VW; V = CH2T; T = CH2, O, S, SO, SO2; W = CO2H, carboxylate ester, carboxamide, etc.], which are substrates for carboxypeptidase G2 for use in antibody-directed enzyme prodrug therapy, producing more active cytotoxic drugs than known products of other carboxypeptidase G2-catalyzed reactions (no data), are prepared Thus, dibenzyl N-[4-[N,N-bis(2-chloroethyl)amino]phenoxycarbonyl]-L-glutamate was hydrogenated, producing N-[4-[N,N-bis(2-chloroethyl)amino]phenoxycarbonyl]-L-glutamic acid.
IT 156079-60-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of antineoplastic prodrugs)
RN 156079-60-6 CAPLUS
CN Benzonitrile, 2-[bis(2-chloroethyl)amino]-5-nitro- (9CI) (CA INDEX NAME)

L9 ANSWER 38 OF 47 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 94309070 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8035424
TITLE: Hypoxia-selective antitumor agents. 9. Structure-activity relationships for hypoxia-selective cytotoxicity among analogues of 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide.
AUTHOR: Palmer B D; Wilson W R; Atwell G J; Schultz D; Xu X Z; Denny W A
CORPORATE SOURCE: Cancer Research Laboratory, University of Auckland School of Medicine, New Zealand.
CONTRACT NUMBER: CM 07321 (NCI)
SOURCE: Journal of medicinal chemistry, (1994 Jul 8) Vol. 37, No. 14, pp. 2175-84.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 25 Aug 1994
Last Updated on STN: 25 Aug 1994
Entered Medline: 18 Aug 1994

AB A series of analogues of the novel hypoxia-selective cytotoxin 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (6) have been prepared and evaluated, in a search for compounds which retain high hypoxic selectivity but have increased potency and/or aqueous solubility. Several analogues with ionizable or dipolar carboxamide side chains showed improved solubility but generally had reduced cytotoxic potency and hypoxic selectivity. Modification of the mustard leaving groups or replacement of the carboxamide moiety provided some compounds with superior potency, but only the mixed chloro/mesylate mustard 20 provided a gain in potency relative to solubility while retaining the hypoxic selectivity of 6. These nitrogen mustards did not show the remarkable activity demonstrated by the related aziridine 7 (CB 1954, 5-(N-aziridinyl)- 2,4-dinitrobenzamide] in Walker 256 adenocarcinoma cells and are not efficient substrates for the DT-diaphorase which activates the latter compound by aerobic nitroreduction in Walker cells. Variations in hypoxic selectivity within the dinitrobenzamide mustards appear not to be due to differences in sensitivity to activation by this enzyme. Walker cells showed intermediate sensitivity to the mono(2-chloroethyl) analogue 26 but not to the related half-mustard 27, suggesting that the inhibition of DT-diaphorase activity is due to steric effects in the 5-position. The preferred compound overall with respect to solubility, potency, and in vitro hypoxic cell selectivity was the (dimethylamino)-ethyl derivative 11. DNA elution studies and comparison of the sensitivity of AA8 and UV4 cells to this compound indicated reductive activation to form a DNA cross-linking agent under hypoxia. Radiobiological studies indicated 11 to be equally active against both aerobic and hypoxic cells in KHT tumors.
It is not clear whether this reflects efficient killing of aerobic cells as a result of diffusion of reduced metabolites from hypoxic regions or whether cytotoxicity in tumors is independent of hypoxia.

L9 ANSWER 38 OF 47 MEDLINE on STN DUPLICATE 9
(Continued)

L9 ANSWER 39 OF 47 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 94252921 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8195036
TITLE: Combining bioreductive drugs (SR 4233 or SN 23862) with the vasoactive agents flavone acetic acid or 5,6-dimethylxanthenone acetic acid.
AUTHOR: Cliffe S; Taylor M L; Rutland M; Baguley B C; Hill R P; Wilson W R
CORPORATE SOURCE: Department of Pathology, University of Auckland School of Medicine, New Zealand.
CONTRACT NUMBER: NCI CM07321 (NCI)
SOURCE: International journal of radiation oncology, biology, physics, (1994 May 15) Vol. 29, No. 2, pp. 373-7. Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 7 Jul 1994
Last Updated on STN: 7 Jul 1994
Entered Medline: 28 Jun 1994

AB PURPOSE: To determine whether 5,6-dimethylxanthenone acetic acid (DMXAA), a potent analogue of flavone acetic acid (FAA) inhibits blood flow in mouse mammary tumors, and to assess whether DMXAA enhances the antitumor effects of Tirapazamine (SR 4233) and the novel bioreductive drug SN 23862 (a dinitrobenbenzene mustard). METHODS AND MATERIALS: MDAH-MCa-4 mouse mammary tumors were grown i.m. in the leg of C3H/HeN mice. Tumor blood flow was assessed by the pertechnetate clearance method and subsequent growth delay was determined in the same tumors. RESULTS: Administration of DMXAA (65-70 mumol/kg) resulted in inhibition of tumor blood flow to approximately 25% of control values, with no recovery observed up to 36 h post-treatment. Combination of DMXAA with SR 4233 provided a significant increase in tumor growth inhibition relative to either drug alone. In this effect, DMXAA was qualitatively similar to FAA, but was approximately 10 x more potent. The interaction between DMXAA (65 mumol/kg) and SR 4233 (200 mumol/kg) was maximal with SR 4233 given between 15 min before and 60 min after DMXAA. For SN 23862, a similar enhanced growth delay was observed in combination with DMXAA, with no obvious time dependence between 15 min before and 4 h after DMXAA. When mean values for groups treated with SR 4233 (200 mumole/kg) alone and in combination with DMXAA (65-90 mumole/kg) were compared, a correlation was observed between tumor blood flow inhibition and subsequent growth delay. CONCLUSION: DMXAA is a potent inhibitor of blood flow in MDAH-MCa-4 tumors. Combination of this vasoactive drug with bioreductive agents leads to an enhanced antitumor effect. For SR 4233 and DMXAA, this enhanced effect may be predictable by measurement of tumor blood flow inhibition shortly after drug

L9 ANSWER 39 OF 47 MEDLINE on STN DUPLICATE 10
(Continued)
administration.

L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:580541 CAPLUS
DOCUMENT NUMBER: 119:180541
TITLE: Nitroaniline derivatives and their use as antitumor agents
INVENTOR(S): Denny, William Alexander; Palmer, Brian Desmond; Wilson, William Robert
PATENT ASSIGNEE(S): Cancer Research Campaign Technology Ltd., UK
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9311099	A1	19930610	WO 1992-GB2199	19921127
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9229526	A	19930628	AU 1992-29526	19921127
AU 666342	B2	19960208		
EP 616609	A1	19940928	EP 1992-923932	19921127
EP 616609	B1	19970618		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07503946	T	19950427	JP 1993-509940	19921127
JP 2987205	B2	19991206		
AT 154591	T	19970715	AT 1992-923932	19921127
ES 2104952	T3	19971016	ES 1992-923932	19921127
CA 2124315	C	20020702	CA 1992-2124315	19921127
US 5571845	A	19961105	US 1994-244449	19940526
US 5750782	A	19980512	US 1996-685079	19960723

PRIORITY APPLN. INFO.: NZ 1991-240785 A 19911128
WO 1992-GB2199 A 19921127
US 1994-244449 A3 19940526

OTHER SOURCE(S): MARPAT 119:180541
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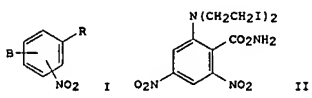
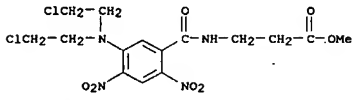


AB Nitroaniline derivs. I [A, R = nitro, cyano, carboxy, carboxamide, etc.; A = (haloalkyl)amino, (sulfonyloxyalkyl)amino] and their uses as pharmaceuticals are claimed. I are active as hypoxia-selective cytotoxins, reductively active prodrugs for cytotoxins, hypoxic cell radiosensitizers, and anticancer agents. Thus, 5-[bis(2-iodoethyl)amino]-2,4-dinitrobenzamide (II) was prepared in several steps. II had cytotoxic

L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
activity in AA8 cells with an IC50 of 34 μM.
IT 150272-13-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for N-(alkyl)nitroaniline derivative (neoplasm
inhibitor))
RN 150272-13-2 CAPLUS
CN β-Alanine, N-[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]-, methyl ester (9CI) (CA INDEX NAME)



IT 142439-61-0P 142439-62-1P 142439-63-2P
150271-87-7P 150271-88-8P 150271-89-9P
150271-90-2P 150271-91-3P 150271-92-4P
150271-93-5P 150271-94-6P 150271-95-7P
150271-96-8P 150271-97-9P 150271-98-0P
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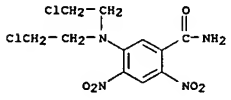
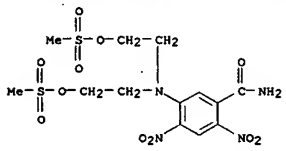
150272-02-9P 150272-03-0P 150272-04-1P
150272-05-2P 150272-10-9P 150272-11-0P
150272-12-1P 150272-37-0P 150272-38-1P
150272-40-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as neoplasm inhibitor)
RN 142439-61-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (CA INDEX NAME)

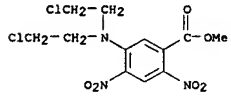


RN 142439-62-1 CAPLUS
CN Morpholine, 4-[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]- (9CI) (CA
INDEX NAME)

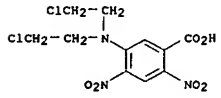
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



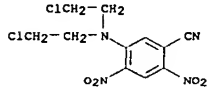
RN 150271-90-2 CAPLUS
CN Benzoic acid, 5-[bis(2-chloroethyl)amino]-2,4-dinitro-, methyl ester (9CI)
(CA INDEX NAME)



RN 150271-91-3 CAPLUS
CN Benzoic acid, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

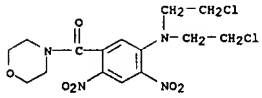


RN 150271-92-4 CAPLUS
CN Benzonitrile, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

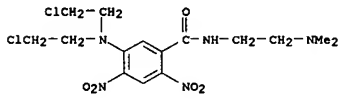


RN 150271-93-5 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-methyl-2,4-dinitro- (9CI) (CA INDEX NAME)

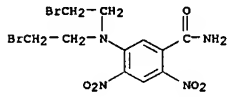
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



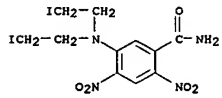
RN 142439-63-2 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 150271-87-7 CAPLUS
CN Benzamide, 5-[bis(2-bromoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

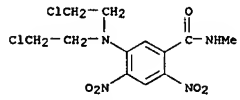


RN 150271-88-8 CAPLUS
CN Benzamide, 5-[bis(2-iodoethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

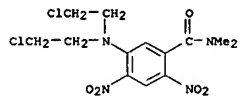


RN 150271-89-9 CAPLUS
CN Benzamide, 5-[bis[2-[(methylsulfonyl)oxy]ethyl]amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

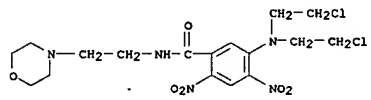
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



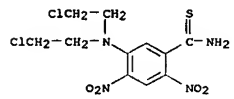
RN 150271-94-6 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N,N-dimethyl-2,4-dinitro- (9CI) (CA INDEX NAME)



RN 150271-95-7 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(4-morpholinyl)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)

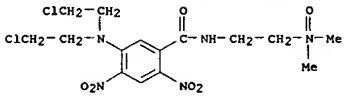


RN 150271-96-8 CAPLUS
CN Benzenecarbothioamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA
INDEX NAME)

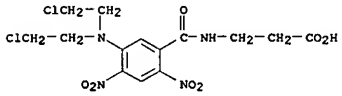


RN 150271-97-9 CAPLUS
CN Benzamide,
5-[bis(2-chloroethyl)amino]-N-[2-(dimethyloxidoamino)ethyl]-2,4-dinitro- (9CI) (CA INDEX NAME)

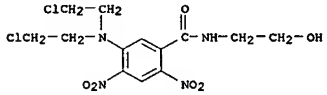
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



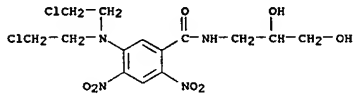
RN 150271-98-0 CAPLUS
CN β-Alanine, N-[5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]- (9CI) (CA INDEX NAME)



RN 150271-99-1 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(2-hydroxyethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

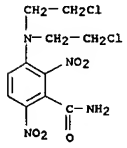


RN 150272-00-7 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-(2,3-dihydroxypropyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

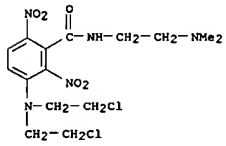


RN 150272-01-8 CAPLUS
CN Benzenesulfonamide, 5-[bis(2-chloroethyl)amino]-2,4-dinitro- (9CI) (CA INDEX NAME)

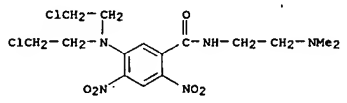
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 150272-05-2 CAPLUS
CN Benzamide, 3-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,6-dinitro- (9CI) (CA INDEX NAME)



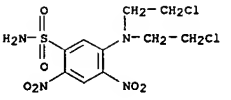
RN 150272-10-9 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,4-dinitro-, monohydrochloride (9CI) (CA INDEX NAME)



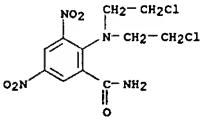
● HCl

RN 150272-11-0 CAPLUS
CN Benzamide, 5-[bis(2-chloroethyl)amino]-N-[2-(dimethyloxidoamino)ethyl]-2,4-dinitro-, monohydrochloride (9CI) (CA INDEX NAME)

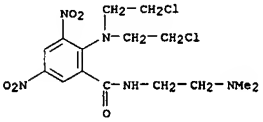
L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 150272-02-9 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-3,5-dinitro- (9CI) (CA INDEX NAME)

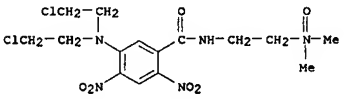


RN 150272-03-0 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-3,5-dinitro- (9CI) (CA INDEX NAME)



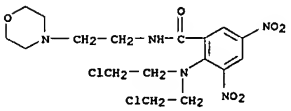
RN 150272-04-1 CAPLUS
CN Benzamide, 3-[bis(2-chloroethyl)amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



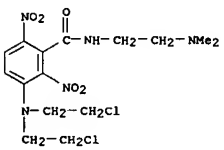
● HCl

RN 150272-12-1 CAPLUS
CN Benzamide, 2-[bis(2-chloroethyl)amino]-N-[2-(4-morpholinyl)ethyl]-3,5-dinitro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

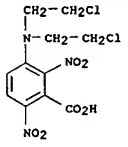
RN 150272-37-0 CAPLUS
CN Benzamide, 3-[bis(2-chloroethyl)amino]-N-[2-(dimethylamino)ethyl]-2,6-dinitro-, monohydrochloride (9CI) (CA INDEX NAME)



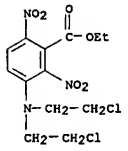
● HCl

RN 150272-38-1 CAPLUS
CN Benzoic acid, 3-[bis(2-chloroethyl)amino]-2,6-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 40 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 150272-40-5 CAPLUS
CN Benzoic acid, 3-[bis(2-chloroethyl)amino]-2,6-dinitro-, ethyl ester (9CI) (CA INDEX NAME)

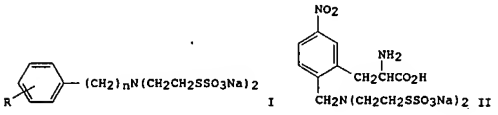


L9 ANSWER 41 OF 47 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 92373730 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1507207
TITLE: Hypoxia-selective antitumor agents. 5. Synthesis of water-soluble nitroaniline mustards with selective cytotoxicity for hypoxic mammalian cells.
AUTHOR: Palmer B D; Wilson W R; Cliffe S; Denny W A
CORPORATE SOURCE: Cancer Research Laboratory, University of Auckland School of Medicine, New Zealand.
CONTRACT NUMBER: CM 07321 (NCI)
SOURCE: Journal of medicinal chemistry, (1992 Aug 21) Vol. 35, No. 17, pp. 3214-22.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 9 Oct 1992
Last Updated on STN: 3 Feb 1997
Entered Medline: 22 Sep 1992

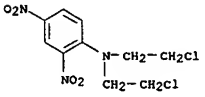
AB Nitroaniline mustards have potential as hypoxia-selective cytotoxic agents, with reductive metabolism activating the nitrogen mustard by converting the electron-withdrawing nitro group to an electron-donating hydroxylamine or amine. However, the parent compounds have poor aqueous solubility, and their potencies are limited by low reduction potentials (E1/2 ca. -600 mV versus the normal hydrogen electrode) and corresponding slow rates of nitro reduction. To address these limitations, a series of 4-nitroaniline mustards bearing hydrophilic side chains attached via an electron-withdrawing carboxamide group was prepared and evaluated for hypoxia-selective cytotoxicity against Chinese hamster cell lines. The N-[(N,N-dimethylamino)ethyl]carboxamide derivatives proved to have excellent aqueous solubility and improved cytotoxic potency, but their reduction potentials, while higher than the non-carboxamide compounds, were still low and little selectivity for hypoxic cells were observed. A series of carboxamides of 2,4-dinitroaniline mustard was also prepared. These compounds had reduction potentials in the desired range (E1/2 ca. -450 mV by cyclic voltammetry) and were more toxic to hypoxic than aerobic UV4 cells. The most selective compounds were 5-[N,N-bis(2-chloroethyl)amino]-2,4-dinitrobenzamide (20, SN 23862) and its water-soluble N-[(N,N-dimethylamino)ethyl]carboxamide analogue. These showed selectivities of 60- to 70-fold for hypoxic UV4 cells. The selectivity of 20 was much superior to that of its aziridine analogue (23, CB 1954), which was only 3.6-fold more toxic to hypoxic than oxic cells in the same system. Compound 20 is a much less efficient substrate than CB 1954 for the major aerobic nitroreductase from rat Walker tumor cells, NAD(P)H:quinone oxidoreductase (DT diaphorase). Lack of aerobic bioactivation of 20 by DT diaphorases may be responsible for its higher hypoxic selectivity than that of 23.

L9 ANSWER 41 OF 47 MEDLINE on STN DUPLICATE 11
(Continued)

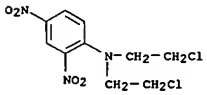
L9 ANSWER 42 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:234428 CAPLUS
DOCUMENT NUMBER: 118:234428
TITLE: Synthesis and radiosensitizing activity of sodium nitroaryliminodiethylthiosulfate and nitro phenylalanine derivatives
AUTHOR(S): Liu, H. X.; Hu, B.; Li, Z.; Mi, F. S.; Shen, Y.
CORPORATE SOURCE: Inst. Radiat. Med., Chin. Acad. Med. Sci., Tianjin, 300192, Peop. Rep. China
SOURCE: Yaoxue Xuebao (1992), 27(8), 632-7
CODEN: YHHPAL; ISSN: 0513-4870
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



AB Title compds. e.g., I (n = 0, 1) and II were synthesized and tested for HeLa-S3 cells in vitro for radiosensitizing activity. Most of them showed various degrees of radiosensitizing activity. The relationship between radiosensitizing effects and chemical structure was discussed.
IT 1221-57-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium thiosulfate)
RN 1221-57-4 CAPLUS
CN Benzenamine, N,N-bis(2-chloroethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

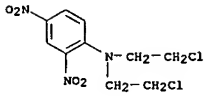


L9 ANSWER 43 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1971:52662 CAPLUS
DOCUMENT NUMBER: 74:52662
TITLE: Mechanism of the reaction of aryl nitrogen mustards with nucleophiles
AUTHOR(S): Benn, Michael H.; Kazmaier, Peter; Watanatada, Churai; Owen, L. N.
CORPORATE SOURCE: Dep. Chem., Univ. Calgary, Calgary, AB, Can.
SOURCE: Journal of the Chemical Society [Section] D: Chemical Communications (1970), (24), 1685-6
CODEN: CCJDAO; ISSN: 0577-6171
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nucleophilic displacement reactions of PhNMeCH2CHMeX, PhNMeCHMeCH2X (e.g., X = Cl), and RC6H4N(CH2CD2Cl)2 (R = H, p-MeO, 2,4-dinitro) involved side chain isomerization via aziridinium ion intermediates. The aziridinium process is competitive with direct displacement and is dominant with weak nucleophiles.
IT 1221-57-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(acetolysis of, mechanism of)
RN 1221-57-4 CAPLUS
CN Benzenamine, N,N-bis(2-chloroethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



L9 ANSWER 44 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1966:51705 CAPLUS
DOCUMENT NUMBER: 64:51705
ORIGINAL REFERENCE NO.: 64:9618b-e
TITLE: Chloroethyl derivatives of 1,2,4-triaminobenzene
AUTHOR(S): Degutis, J.; Bieksa, V.
CORPORATE SOURCE: Polytech. Inst., Kaunas, Lithuania
SOURCE: Zhurnal Organicheskoi Khimii (1965), 1(11), 1936-41
CODEN: ZORKAE; ISSN: 0514-7492
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Heating N,N-bis-(2-hydroxyethyl)-2,4-dinitroaniline (I) with excess POCl3 0.5 hr. at 80-90° gave after an aqueous treatment 90% N,N-bis(2-chloroethyl) analog (II), m. 117-18. II reduced with SnCl2 in concentrated HCl at room temperature, neutralized with Na2CO3, extracted with Et2O, and the extract treated with HCl gave 70% 1-[N,N-bis(2-chloroethyl)]-1,2,4-triaminobenzene-2HCl (III), decomposed at 150°. III neutralized with aqueous Na2CO3, extracted with Et2O, and the extract treated with Ac2O, followed by dry HCl, gave 79% 2,4-diacetamido analog mono-HCl salt, decomposed at 73-85°. I in 80% hot EtOH was slowly treated with Na2S and S in H2O and refluxed 4 hrs. to yield 84% 2-amino-4-nitro-N,N-bis(2-hydroxyethyl)aniline (IV), m. 105-6°. IV with Ac2O in hot H2O gave the 2-acetamido analog, m. 129.5-30.5°, which heated 1 hr. with SOCl2 in (CH2Cl)2 gave after solution in hot MeOH and dilution with H2O 81% 2-acetamido-4-nitro-N,N-bis(2-chloroethyl)aniline (V), m. 119-20°. V with SnCl2 in concentrated HCl stirred until dissolved, then chilled to 0° for 0.5 hr. and evaporated in vacuo, gave a residue which taken up in H2O and treated with H2S, filtered, gave on evaporation 55% N,N-bis(2-chloroethyl)-2-acetamido-4-aminoaniline, isolated as HCl salt, decomposed above 170°. MeO2CCH2NH2.HCl in EtOH treated with Na2CO3, filtered, and treated with 2,4-(O2N)2C6H3Cl 5 hrs. at reflux gave 90% 2,4-(O2N)2C6H3NHCH2CO2Me, m. 114-15°, which treated with Na2S and S in aqueous EtOH 5 hrs. gave 53% 7-nitro-2-oxo-1,2,3,4-tetrahydroquinoxaline (VI), which did not have a definite m.p., and 10% more soluble (in AmOAc), N-2-amino-4-nitrophenylglycine Me ester, m. 197-9°, red solid. The latter kept with ethylene oxide in 50% AcOH 1 day gave 81% 4,2-O2N[(HOCH2CH2)2N]C6H3N(CH2CO2Me)CH2CH2OH, m. 89-90° a red solid.
IT 1221-57-4P, Aniline, N,N-bis(2-chloroethyl)-2,4-dinitro-
RL: PREP (Preparation)
(preparation of)
RN 1221-57-4 CAPLUS
CN Benzenamine, N,N-bis(2-chloroethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)

L9 ANSWER 44 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



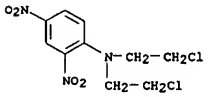
L9 ANSWER 45 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1961:98981 CAPLUS
DOCUMENT NUMBER: 55:98981
ORIGINAL REFERENCE NO.: 55:18575e-i,18576a-c
TITLE: Cancerocidal substances. XXXI. Antitumor action of 1-dialkylamino-2,3-dichloropropanes and 2-dialkylamino-1,3-dichloropropanes
AUTHOR(S): Kuwada, Yutaka
CORPORATE SOURCE: Pharmacol. Research Foundation, Tokyo
SOURCE: Chemical & Pharmaceutical Bulletin (1960), 8, 807-14
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB To examine their possible bifunctional alkylation, R2NCH2CHClCH2Cl (I) and R2NCR'(CH2Cl)2 (II) were prepared, and their chemical and biol. properties studied. In general, heating equimolar amts. of R2NH and glycidol gave R2NCH2CH(OH)CH2OH (III) [weight R2NH used, yield (g.) and m.p. III given]: - morpholine, -(b6 152-4°); 36 g. dicyclohexylamine, 44, 74-5°; 25 g. (PhCH2)2NH, 32, 47-8°; and 21 g. (HOCH2CH2)2NH, 38, b0.02 190-5°. Refluxing III 2 hrs. with SOCl2 in CHCl3 gave I.HCl (R, m.p. I.HCl, and m.p. I picrate given): Me, 165-6°, 101-2°; Et, -, 96-7°; Bu [b7 120-4° (free I)], -, 94-5°; morpholino, 115° (decomposed at 190°), [b3 104-6° (free I)], 89-90°; cyclohexyl, 159-60°, 129-30°, PhCH2, 154-5°, -; and HOCH2CH2, -, [b7 145-6° (free I)], 67-8° (picrylsulfonate, m. 157-8°). Et2NCH2CH:CH2 (1.5 g.) brominated with Br in CCl4 as usual yielded with picric acid 4 g. Et2NCH2CHBrCH2Br picrate, m. 89-90°; picrylsulfonate m. 143-4°. I (R = Et) (33 g.) oxidized with 30% H2O2 in Ac2O by the previously described method (CA 49, 8304h) gave 2,2-diethyl-4-chloroisoxazolidinium salt (IV), purified as the picrate, m. 145-6°. Thus, the desired N-oxide of I (R = Et) was not obtained, and IV showed no antitumor activity. Closely related to I were RN(CH2CHClCH2Cl)2 (V), prepared from RN[CH2CH(OH)CH2OH]2 (VI) and SOCl2 in CHCl3, as above (R, b.p. VI, b.p. V, m.p. salts of V given): Me, -, b6 141-2°, HCl salt m. 123-4°, picrate m. 78-9°; and Et, b0.02 175-6°, b7 137-9°, -. Since I and V showed only slight antitumor activity in vivo, although they exhibited bifunctional activity in vitro, II were synthesized to test the effect of the greater distance between the Cl atoms. Et2NH (36 g.) with 58 g. BrCH(CO2Et)2 in EtOH yielded 25 g. Et2NCH(CO2Et)2, b8 110-13°, and this (10 g.) reduced with LiAlH4 in ether yielded 3.5 g. Et2NCH(CH2OH)2 (VII), b0.1 110°. Methylation of H2NCMe(CH2OH)2 gave Me2NCMe(CH2OH)2, and chlorination of this and VII with SOCl2 gave, resp., II (R = R' = Me), m. 126-7° (picrate, m. 156-7°), and II (R = Et, R' = H), picrate m. 91-2°. Again, the rate of alkylation in vitro led to expectation of antitumor activity in vivo, but no such activity was shown. Further compds. related to the preceding were synthesized and similarly tested: Et2NCH2CHClMe.HCl, m. 100-1°, picrate m. 126-7°; MeN(CH2CHClMe)2.HCl (VIII), m. 104°, picrate m. 107°; IIN(CH2CHClMe)2.HCl, m. 200-1°; N(CH2CHClMe)3.HCl (Wilson and Tishler, CA 46, 1972a), m. 126-7°, picrate m. 127-8°; (ClCH2CH2)2NCH2CHClMe (IX) (Ford-Moore, et al., CA 41, 691h), b5 106-7°, HCl salt m. 72-3°, picrate m. 80-1°;

L9 ANSWER 45 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
[(MeCHClCH2)2NCH2]2.2HCl (X), m. 159-60°, picrate m. 125-6°; 2,4-(O2N)2C6H3N(CH2CH2Cl)2 (XI), m. 119°; and PhCHMeN(CH2CH2Cl)2, picrate m. 130-1°. VIII and IX treated with 30% H2O2 in Ac2O contg. AcONa were converted to their N-oxides, picrates m. 109-10° and 102-3°, resp., and HCl salts m. 117-18° and 111-12°, resp. X was prepd. by chlorination, as above, of [(MeCH(OH)CH2)2NCH2]2, b0.05 165°, which (35 g.) was in turn prepd. by heating 50 g. [MeCH(OH)CH2]2NH 30 hrs. at 100-20° with (CH2Br)2 and K2CO3. XI (0.2 g.) was prepd. by stirring 0.4 g. 2,4-(O2N)2C6H3F 2 hrs. with (ClCH2CH2)2NH.HCl and NaHCO3 in EtOH. MeSO2OCH2CH2Cl (3 g.), b15 138-9°, was prepd. by adding 3.6 g. MeSO2Cl dropwise at 0° to 6 g. HOCH2CH2Cl in C5H5N, but it failed to show the antitumor activity reported by Haddow and Ross (CA 50, 14102e). Thiosulfate consumption and Cl- liberation were measured as previously described (CA 53, 215e) for all these compds., and their mode of alkylation and hydrolysis in vitro discussed.

IT 1221-57-4P, Aniline, N,N-bis(2-chloroethyl)-2,4-dinitro-
RL: PREP (Preparation)
(preparation of)

RN 1221-57-4 CAPLUS

CN Benzenamine, N,N-bis(2-chloroethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



L9 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1952:67181 CAPLUS
DOCUMENT NUMBER: 46:67181
ORIGINAL REFERENCE NO.: 46:11240h-i,11241a-e
TITLE: Sulfonyl esters of bis(2-hydroxy-alkyl)arylamines
INVENTOR(S): Timmis, Geoffrey M.
PATENT ASSIGNEE(S): Wellcome Foundation Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 662645		19511212	GB	

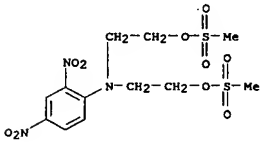
AB These esters, related to the nitrogen mustards, are prepared from the sulfonyl chloride and the alc. in the presence of pyridine. These substances are active against malignant tumors and blood diseases. PhN(CH2CH2OH)2 (I) 13.5, with p-MeC6H4SO2Cl (II) 30 yields N,N-bis[2-(p-tolylsulfonyloxy)ethyl]aniline 12.8 g., m. 89-90° (from MeOH). I 1.8 g. with PhSO2Cl 2.6 cc. gives N,N-bis[2-(phenylsulfonyloxy)ethyl]aniline 1.2 g., m. 64-5° (from MeOH). N,N-bis(2-hydroxyethyl)-2-naphthylamine 2.3 with II 4 g. gives N,N-bis[2-(p-tolylsulfonyloxy)-ethyl]-2-naphthylamine 0.9 g., fine white crystals from MeOH, m. 113-14°. I 1.8 with 4,3-Me(O2N)C6H3SO2Cl 4.7 g. gives N,N-bis[2-(4-methyl-3-nitrophenylsulfonyloxy)ethyl]aniline 3.7 g., m. 149° (from CHCl3). N,N-Bis(2-hydroxyethyl)-p-anisidine (III) 13.5 with II 23.4 gives N,N-bis[2-(p-tolylsulfonyloxy)ethyl]-p-anisidine 13.5 g., m. 92-3° (after 3 recrystns. from MeOH). III 3.3 g. with p-MeOC6H4SO2Cl (IV) 8.0 gives N,N-bis[2-(p-methoxyphenylsulfonyloxy)ethyl]-p-anisidine 6.7 g., m. 105-6° (from CHCl3-petr. ether). I 3.6 with p-ACNHC6H4SO2Cl 10 gives N,N-bis[2-(p-acetamidophenylsulfonyloxy)ethyl]aniline, m. 115° (from MeOH), decompose 215°. I 3.0 with IV 6.6 yields N,N-bis[2-(p-methoxyphenylsulfonyloxy)ethyl]aniline 4.2 g., m. 87-8° (from CHCl3-petr. ether). N,N-Bis[2-(2-hydroxyethyl)-2-naphthylamine 2.3 with IV 4.3 yields N,N-bis[2-(p-methoxyphenylsulfonyloxy)ethyl]-2-naphthylamine 3.5 g., m. 143-4° (from MeOH); recrystn. from CHCl3-petr. ether gave material m. 146°. p-ClC6H4N-(CH2CH2OH)2 (V) 2.1 with IV 4.5 g. gives N,N-bis[2-(p-methoxyphenylsulfonyloxy)ethyl]-p-chloroaniline 4.4 g. from MeOH; recrystn. from CHCl3-petr. ether yields 3.7 g. material, m. 103-4°. 2,4-(O2N)C6H3N(CH2CH2OH)2 2.7 g. with II 4.3 give N,N-bis[2-(p-tolylsulfonyloxy)ethyl]-2,4-dinitroaniline (VI), m. 116-17° (from CHCl3-petr. ether). V 21.5 with II 40 gives N,N-bis[2-(p-tolylsulfonyloxy)ethyl]-p-chloroaniline 23.5 g., m. 103-4° (from Me2CO-petr. ether). VI 2.7 g. with MeSO2Cl 1.53 cc. gives N,N-bis[2-(methylsulfonyloxy)ethyl]-2,4-dinitroaniline 2.6 g., m. 108° (from Me2CO-petr. ether) V 4.3 with p-AcNHC6H4SO2Cl gives N,N-bis[2-(p-acetamidophenylsulfonyloxy)ethyl]-p-chloroaniline (VII) 5.8 g. (from Me2CO-petr. ether), softens 160°, m. 201° (decomposition). VII 3 g. with HCl in MeOH gives N,N-bis[2-(p-aminophenylsulfonyloxy)ethyl]-p-chloroaniline 1.3 g. (from Me2CO, softens 124°, m. 260°; I 1.65 with o-O2NC6H4SO2Cl 4.0 gives N,N-bis[2-(o-nitrophenylsulfonyloxy)ethyl]aniline, m. 200° (from MeOH). I 1.8

L9 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
with 2-C10H7SO2Cl 4.6 gives N,N-bis[2-(2-naphthylsulfonyloxy)ethyl]aniline 4.2, on recrystn. m. 114-15°, after 2 recrystns. from CHCl3-petr. ether, 114-115°. V 2.2 with 2-C10H7SO2Cl 4.7 gives N,N-bis[2-(2-naphthylsulfonyloxy)ethyl]-p-chloroaniline 3.2 g., m. 164° (from dioxane-MeOH). p-ClC6H4NH2 91.5 g. heated 3.5 hrs. with MeCH(OH)CH2OH at 170-180° gives p-(MeCHOHCH2)2NC6H4Cl (VIII) 60 g., m. 112° (from petr. ether). VIII 9.6 with II 16 gives 7.5 g. bis(p-tolylsulfonyl) deriv. (from CHCl3) which, recrystd. from Me2CO-petr. ether, m. 161°. From the CHCl3 mother liquid is obtained material m. 135° (from Me2CO-petr. ether), probably p-(p-MeC6H4SO2OCMe2)2NC6H4Cl.

IT 500896-22-0P, Methanesulfonic acid, diester with 2,2'-(2,4-dinitrophenyliminodiethanol
RL: PREP (Preparation)
(preparation of)

RN 500896-22-0 CAPLUS

CN Ethanol, 2,2'-[(2,4-dinitrophenyl)imino]bis-, dimethanesulfonate (ester) (9CI) (CA INDEX NAME)



L9 ANSWER 47 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1949:41353 CAPLUS
DOCUMENT NUMBER: 43:41353
ORIGINAL REFERENCE NO.: 43:7442g-i,7443a-h
TITLE: Aryl-2-haloalkylamines. I
AUTHOR(S): Ross, W. C. J.
SOURCE: Journal of the Chemical Society (1949) 183-91
CODEN: JCSOA9; ISSN: 0368-1769
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

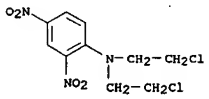
AB RN(CH2CH2OH)2 or RNHCH2CH2OH were prepared by heating 1 mol. RNH2 and 2 mols. (CH2)2O (with C6H6 as diluent in some cases) 16 h. at 90° or 150°; 2-aminofluorene and p-H2NC6H4CH:CHPh give monosubstitution products at 90°, and the latter a disubstitution product at 150°; p-ClC6H4NH2 gives a disubstitution product at the higher temperature, whereas o-MeC6H4NH2 gives a monosubstitution product and o- and m-ClC6H4NH2, 2,5-Cl2C6H3NH2, and o- and p-O2NC6H4NH2 do not react. o-C6H4(NH2)2 reacts vigorously at 90° but (p-H2NC6H4)2, (o-MeC6H3NH2)2, and (o-MeOC6H3NH2)2 require a temperature of 150° for reaction. RN(CH2CH2OH)2 were prepared also by refluxing (7-30 h.) 0.5 mol. RNH2, 2.5 mols. HOCH2CH2Cl, and 0.7 mol. CaCO3 in 500 cc. H2O; the filtrate is saturated with NaCl and extracted with ether; both mono- and disubstitution products are formed; 320 g. PhNH2 yields 120 g. PhNHCH2CH2OH and 330 g. PhN(CH2CH2OH)2. p-MeOC6H4NH2 and 1 mol. HCOCH2CH2Cl give only N-2-hydroxyethyl-p-anisidine, m. 44-5°; PhNH2 yields mainly 1,4-diphenylpiperazine. RN(CH2CH2Cl)2 are prepared by adding 1 mol. RN(CH2CH2OH)2 to 1.2 mols. PCl5 in 1 l. CHCl3 (refluxed 1 h.) or by slowly adding it to 2 mols. POCl3 and heating 0.5 h. on the steam bath. RN(CH2CH2Br)2 were prepared with 3 mols. PBr3; with NaI in Me2CO they yield RN(CH2CH2I)2. PhEtNCH2CH2Cl yields a picrate, m. 110°. N,N-Bis(2-bromoethyl)aniline, m. 53-5°. N,N-Bis(2-hydroxyethyl)-o-toluidine picrate, m. 110 °; 2-chloroethyl compound, m. 92°. N,N-Bis(2-hydroxyethyl)-m-toluidine, m. 72-3°; 2-chloroethyl compound, m. 33° (picrate, m. 113°); 2-bromoethyl compound, m. 42°; 2-iodoethyl compound, m. 61-2°. N,N-Bis(2-hydroxyethyl)-p-toluidine, m. 53-4°; 2-chloroethyl compound, m. 43-5° (picrate, m. 72-3°); 2-bromoethyl compound, m. 62-3°; 2-iodoethyl compound, m. 69°. N,N-Bis(2-chloroethyl)-o-anisidine picrate, m. 104°; N,N-bis(2-bromoethyl)-p-anisidine, m. 47-9°; 2-iodoethyl compound, m. 40°. p-Chloro-N,N-bis(2-hydroxyethyl)aniline, m. 95-6° (picrate, m. 122-3°); 2-chloroethyl compound, m. 74-5° (picrate, m. 147-9°); 2-bromoethyl compound, m. 67-8°; 2-iodoethyl compound, m. 106°. o-Biphenylyl (2-hydroxyethyl)amine picrate, m. 155-6°; the Cl compound could not be prepared p-Biphenylyl-bis(2-hydroxyethyl)amine, m. 149-51°; 2-chloroethyl compound, yellow, m. 106-7°. 2,4-Dinitro-N,N-bis(2-chloroethyl)aniline, yellow, m. 116-18°. 1-Naphthylbis(2-hydroxyethyl)amine (picrate, m. 161-3°); the 2-chloroethyl compound is an oil. 2-Naphthylbis(2-hydroxyethyl)amine, m. 96-8° (picrate, m. 134-6°); 2-chloroethyl compound, m. 52-5° (picrate, m. 102°). N,N-Bis(2-chloroethyl)-p-aminobenzoic acid, m. 168-9° (prepared from the aldehyde and KMnO4). N-2-Hydroxyethyl-p-aminostilbene, m. 158-9°; 2-chloroethyl compound, m. 135°. N,N-Bis(2-hydroxyethyl)-p-aminostilbene, m. 150-2°; 2-chloroethyl compound, m. 126°; this was prepared also

L9 ANSWER 47 OF 47 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
from p-(ClCH2CH2)2NC6H4CHO and PhCH2MgCl. N-2-Hydroxyethyl-2-aminofluorene, m. 144-6°; 2-chloroethyl compd., m. 127-9°. N,N,N',N'-tetrakis(2-chloroethyl)-p-ph-enylenediamine, m. 79-80°; the corresponding tetra-HO compd. is very unstable and darkens rapidly in air. N,N, N',N'-Tetrakis(2-hydroxyethyl)benzidine, m. 174-6°; 2-chloroethyl compd., m. 125-6°; 2-bromoethyl compd., m. 145°. N,N,N',N'-Tetrakis(2-hydroxyethyl)-o-tolidine (dipicrate, m. 202° (decompn.)); 2-chloroethyl compd., m. 72-3°. N,N,N',N'-Tetrakis(2-hydroxyethyl)-o-dianisidine (dipicrate, m. 195° (decompn.)); 2-chloroethyl compd., m. 81-2°. A no. of the halogen compds. exhibit a remarkably strong photoluminescence. Most of the compds. are light-sensitive and develop deep colors on exposure to air, esp. in dil. soln. The rate of hydrolysis at 37° in Me2CO-H2O of PhN(CH2CH2Cl)2, m- and p-MeC6H4N(CH2CH2Cl)2, 2-C10H7N(CH2CH2Cl)2, and p-MeOC6H4N(CH2CH2Cl)2, as measured by the liberation of H or Cl ions, is practically unimol. with respect to the amine; the rate of disappearance of the amine is greater in the presence of Na2S2O3. The reaction is of the SN 1 type and the rate-detg. step is the initial ionization of the amine. For substituted PhN(CH2CH2Cl)2 the rates of hydrolysis vary in the order o-MeO > o-Me > p-MeO > p-Me > m-Me > H > p-Ph > o-Ph > p-Cl > p-CHO, p-CO2H, and 2,4-(NO2)2. With 2 exceptions (derivs. of o-MeC6H4NH2 and o-MeOC6H4NH2) the order of the rates of hydrolysis is the same as the order of basicities of the parent RNH2. The rate of hydrolysis of PhN(CH2CH2Cl)2 is considerably less than that of PhNEtCH2CH2Cl. The Br compds. hydrolyze more rapidly than the Cl compds. and the iodo compds. decomp. at an even faster rate. A no. of the halogen compds. show a marked cytotoxic effect on tumors (to be reported elsewhere) and the more rapidly hydrolyzed compds. have a vesicant action.

IT 1221-57-4P, Aniline, N,N-bis(2-chloroethyl)-2,4-dinitro-
RL: PREP (Preparation)
(preparation of)

RN 1221-57-4 CAPLUS

CN Benzenamine, N,N-bis(2-chloroethyl)-2,4-dinitro- (9CI) (CA INDEX NAME)



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